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PROGRAMS

of

NATIONAL INSTITUTES OF HEALTH

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Public Health Service

Programs of the

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PROGRAMS OF THE NATIONAL INSTITUTES OF HEALTH

General

Functions and responsibilities

The National Institutes of Health, a bureau of the Public Health Service, supports medical research, research training, and construction of research facilities in universities, medical and dental schools, and other non-Federal research centers. It also conducts research in its own laboratories and clinical facility in Bethesda, Md., and in the field. In the search for means to better health and control of disease, it pursues a broad-scale, scientific approach to increased knowledge of biological processes. In the field of mental health, its activities, under the National Institute of Mental Health, include assistance to the States in developing community mental health services (See section J).

Early history

The first research laboratory in the Public Health Service, and the forerunner of today's National Institutes of Health, was established in the Public Health Service Hospital (formerly Marine Hospital) on Staten Island, N.Y., in 1887. Following the concepts and techniques of European bacteriology, research in this early Public Health Service laboratory concentrated on combating of imported communicable diseases -- notably, at that time, cholera, smallpox, yellow fever and bubonic plague.

This early laboratory was moved in 1891 to Public Health Service headquarters in Washington, D.C., and named the Hygienic Laboratory. It rapidly became a major force in the Nation's scientific attack upon disease, and was responsible for notable research accomplishments. The Reorganization Act of 1902 (P.L. 57-236) authorized the Public Health and Marine Hospital Service to strengthen and expand its bacteriological studies and established an advisory board of experts (today's National Advisory Health Council). On the same day, July 1, 1902, the Biologics Control Act (P.L. 57-244) was passed. This gave the Hygienic Laboratory authority to control the purity, safety, and potency of commercial biologic products sold in interstate commerce. The Reorganization Act also provided that if no commissioned medical officers were available, the Public Health Service could employ "competent persons to take charge of the divisions of chemistry, zoology, and pharmacology." This provision made possible the development of a staff of scientists distinguished in the basic disciplines as well as of those especially skilled in public health service per se.

Although the early mission of the Hygienic Laboratory was related primarily to research in control of communicable and infectious diseases, it is significant that emphasis in many areas was given to fundamental investigations. In 1922 the annual report of the Surgeon General pointed out that "it has been the policy to have the work of the Hygienic Laboratory guided into channels of fundamental research so far as practicable and this has been carried forward with most gratifying results during this year."

During the decade immediately following World War I, there were relatively few outstanding centers of medically oriented research. The Hygienic Laboratory was in the forefront of this group, which included the Rockefeller Institute, the Carnegie Institution's biological component, the Johns Hopkins School of Medicine, Harvard Medical School, and the

University of Pennsylvania. Three great accomplishments of the Hygienic Laboratory during this period were: 1. the establishment of the sciences of biochemistry and physical chemistry as basic to biomedical research; 2. establishment of the scientific basis of nutrition; and 3. advances in control of many major infectious diseases.

It was at the Hygienic Laboratory during the period 1920-1927 that Professor William Mansfield Clark and his colleagues of the chemistry division carried out their classic studies on biologic oxidation and reduction, on which all of modern biochemistry rests. During this same period, fundamental observations on cell permeability and on the correlation of chemical, electrical, and functional changes in living cells were made in the pharmacology division under the direction of Professor Carl Voegtlin.

Joseph Goldberger's discovery of the cause and cure of pellagra (1915-1923) -- through research undertaken because at that time it appeared to be a communicable disease -- was another Hygienic Laboratory accomplishment of far-reaching importance, not only in itself but because it opened an era of research leading to conquest of nutritional deficiency diseases.

Meanwhile, research on infectious diseases went forward with notable success. Early gains were made in anaphylaxis and in the concept of allergy. Safety of diphtheria antitoxin and of smallpox vaccination was achieved. A method for making rabies vaccine generally available was developed. Important studies of plague were carried out, tularemia was identified, a successful vaccine against Rocky Mountain spotted fever was made.

New research trends

During the 1920's, Public Health Service officials recognized that greater control over the communicable diseases and increased life span augmented the threat of cancer, cardiovascular diseases, and other chronic and degenerative disorders to the American people. The research programs of the National Institutes of Health, created from the Hygienic Laboratory by Act of Congress in 1930 (P.L. 71-251) began, accordingly, to shift their direction and dimension. By the mid-thirties, a much broader disease-oriented research mission was given to the NIH. This was first signalized publicly by the establishment of the National Cancer Institute in 1937. The move of NIH, the following year, to Bethesda, through a gift of land by Mr. and Mrs. Luke Wilson, made possible a much broader base of operation.

Toward the end of World War II, the public had come to accept the practical value of continued research. At the same time, the scientific community recognized the increasing need for a large-scale, Federally sponsored attack on chronic and degenerative disease. High-level discussions led to the Bush and Steelman reports, which, in turn, led to the establishment of the National Science Foundation. The NSF was originally conceived as the single source in Government from which broad support of science would flow. During the long delay between conception and establishment of NSF, NIH research followed a natural course of expansion that eventually embraced across-the-board programs, providing an underpinning of support in the relevant fundamental sciences. Such an established research structure eventually shifted the emphasis of NSF programs.

The nature of the programs the NIH now supports thus reflects the hierarchy of the NIH in the late 1940's and, in turn, the concept of the late 1920's of a mission-oriented operation which had to cover both fundamental and applied research. The authorization in the National Cancer Institute Act for support of research and research training in non-Federal institutions set the pattern for the other disease-oriented programs of the National Institutes of Health. The pluralizing of the name followed establishment of the National Heart Institute, the National Institute of Dental Research, and the Experimental Medicine and Biology Institute (since reorganized into the Institute for Allergy and Infectious Diseases; a Division, now Institute, of General Medical Sciences; and the Division of Biologics Standards). An important initial step in the development of the support program of the NIH was taken in 1947 when certain grants of the war-time Office of Scientific Research and Development were turned over to the NIH.

During the late forties and early fifties the growth of NIH and its programs was characterized by particular concern with problems of heart disease, cancer, and mental health. In 1949 the mental hygiene program of the Public Health Service was transferred to NIH and became the National Institute of Mental Health. These were, and remain, the fields in which substantial increases in appropriations for research have been made.

1956-"Year of Decision"

The year 1956 is significant because in that year very deliberate decisions were made both in the executive branch and the Congress which resulted in the expansion of the NIH programs and of medical research generally. In the executive branch initial action was taken to provide budget support commensurate with the opportunity for productive research that would meet the test of excellence and to take advantage of the full measure of available research capabilities. This step was given further impetus by the Congress through which, in addition to full support of current research, emphasis was directed toward enlarging the national base for medical research through increased manpower, facilities, and institutional capabilities.

These decisions engendered specific actions, such as the passage of the Health Research Facilities Construction Act (P.L. 85-835) to enable institutions to enlarge, renovate, or construct new buildings and laboratories for research. This action was particularly necessary because, following World War II and the Korean conflict, most institutions were operating in buildings no longer adequate, in either size or equipment, for increased and sophisticated modern medical research.

In order to increase biomedical research manpower throughout the nation, programs for training grants to institutions, at the graduate and postgraduate level, were expanded with Congressional support.

In addition to increased facilities and manpower for medical research, it was apparent that action to strengthen and enlarge institutional capability for health research was also necessary. To meet this need a number of programs were instituted, as follows:

1. General Research Support Grants (authorized under P.L. 86-798) were made available to schools of medicine, dentistry, public health and osteopathy, in order to make funds available on a broader basis than through individual research project grants.

2. Technical resources for expanding research programs were made available

through support for development of regional primate research centers and centers for research in biomedical engineering and the application of computers to biology and medicine.

3. The Fellowship Program was extended to provide for Research Career Awards and enlarge opportunities for full-time research.

4. To fill a major gap in facilities and capabilities for clinical research, funds were made available for support of general and categorical clinical research centers.

5. Steps were taken to provide purposefully for relating the strong development of medical research in this country to that of other nations to secure the full advantages of unique research opportunities and capabilities existent abroad.

It became apparent in the late fifties that much research of a non-categorical nature needed support and, indeed, only through greater effort in this area would it be possible to produce basic knowledge on which to build categorical and further applied research. As a consequence the Division of General Medical Sciences was established in 1958. Growing appreciation of the importance of this fundamental research and of the increasing role of such research programs led to elevation of the Division to Institute status in 1963 (See section H).

Meanwhile it was apparent that inadequate attention within the NIH categorical structure was being given to biomedical problems of aging and to the broad important area of child health and human development. This led to the establishment, in 1963, of the National Institute of Child Health and Human Development (See section F).

Organization for Research

Direct operations

The solitary laboratory of bacteriology, through a series of organizational changes evolved into the four Divisions of the Hygienic Laboratory: Pathology and Bacteriology; Zoology; Chemistry; and Pharmacology. The change to a disease-oriented mission and the establishment of the several Institutes perpetuated the organization by scientific disciplines with such modifications as became necessary to meet the shifting concepts of biomedical research. The broadened NIH mission made apparent the need for facilities in which clinical research could be carried on in greater depth and on more particularized problems than was possible at most medical schools, which had teaching and service as well as research functions. To meet this need, the 516-bed Clinical Center was established at the NIH in 1953 (See section L).

The development of a comprehensive environment which included clinical research was an expression of very early appreciation within the Public Health Service of the need not only to find means of supporting science within the universities but as part of a general thrust toward a wholly new concept of support of excellence. The emphasis on centers of excellence led, on the one hand, to the NIH intramural operation as it is today, and, on the other, to the rapid growth of the extramural program, which fostered the development of excellence. Development of the extramural program necessitated a geographic base of competence across the Nation. In consequence of this policy, many institutions were enabled, through NIH support, to expand their research potential and to develop stature as centers of research excellence equivalent to that of those already established centers in the Massachusetts, New York, Baltimore and California areas.

Central Direction and Coordination

Policy development and scientific direction

Overall policy development and scientific direction are the responsibility of the Director, NIH. It is significant that, from the beginning the PHS has selected the director on the basis of recognized competence in scientific research. Leadership from the scientific, rather than from the purely administrative, area has permitted a series of categorically oriented programs to develop in such a way that the aggregate thrust of all our institutions of learning has been more purposeful than would otherwise have been possible.

Advice in policy development and scientific direction is given by the Institute Directors, Scientific Directors, and Clinical Directors. These groups meet regularly with the Director or his Deputy and the Director of Laboratories and Clinics.

Grants management

The extent of NIH grants and awards for research and research training has required special organizational structures. One of these is the Division of Research Grants (See section P) which is responsible for the review and approval activities. A special grants audit section operates under the Chief of the Financial Management Branch. Under the policy of giving contracts, instead of grants, to profit-making organizations, a research contracts section has been established in the Supply Management Branch of the Office of the Director.

Program planning

Sound direction of the many activities of the NIH requires continuous survey and analysis of these activities and their impact on medical research nationally and on the total national commitment to research and development, as well as to legislative action relating to research. These activities in the Office of the Director are carried out by the Office of Program Planning.

OD organizational chart here.

THE NATIONAL CANCER INSTITUTE

Origin and Development

The National Cancer Institute was established within the Public Health Service by an Act of Congress approved August 5, 1937. It was the first unit of the federal health agency assigned to categorical disease research, and became the prototype of the Institutes now administered as the National Institutes of Health.

By the mid-thirties, reduction of mortality from many infectious and communicable diseases led medical scientists and forward-looking health administrators and legislators to realize that the chronic and degenerative diseases, such as cancer, heart conditions and arthritis, would pose the main threat to an aging population and would therefore become the next important area for medical research.

Early Efforts

Throughout medical history, progress against the family of malignant diseases called cancer had been paltry and discouraging. Even with the arrival of the twentieth century a diagnosis of cancer was still virtually a death warrant for the patient. Research efforts to understand the nature of cancer as a problem of disorderly growth of cells and tissues in the body had been going on for many years, but on a small scale with little organization or support. In 1913 a group of physicians in New York formed the American Society for the Control of Cancer (later to become the

American Cancer Society), and in 1922 the Public Health Service undertook to investigate cancer as a part of its general program of research. Through such efforts important new knowledge began to build up, but the pace was slow.

Efforts to create a federal cancer research institute and thus apply the authority and resources of the Government to a large-scale approach to the problem had been made in several quarters prior to enactment of the 1937 measure. That legislation was the final outcome of three bills and a House joint resolution introduced in the first session of the 75th Congress. The first two bills, which were identical, were introduced on April 2, 1937 by Senator Homer T. Bone and Rep. (now Senator) Warren G. Magnuson of Washington. On April 29 Rep. Maury Maverick of Texas introduced a bill which largely represented the culmination of persistent efforts by the late Dr. Dudley Jackson, a surgeon of San Antonio, on behalf of a national cancer institute. On June 24 Rep. John F. Hunter of Ohio introduced a House joint resolution containing the same provisions as the Maverick bill except that it would have made the proposed institute a memorial to Thomas Jefferson.

The bill introduced by Senator Bone was distinguished by receiving the signature of every member of the Senate. This bill called for initial appropriation of $2.4 million, and an annual appropriation thereafter of $1 million. Its companion measure in the House met no real opposition. Together with the Hunter House joint resolution, it was referred to the Committee on Interstate and Foreign Commerce.

All bills for the establishment of a national cancer institute were considered at a joint hearing conducted on July 8, 1937 by a cancer subcommittee composed of five Senators and six Representatives which was chaired by Senator Copeland. The hearing lasted one day and resulted in a revised bill which was passed by both houses before the end of July.

Provisions of the Act

The National Cancer Institute Act authorized and directed the Surgeon General of the Public Health Service to:

(a) Conduct, assist, and foster researches, investigations, experiments, and studies relating to the cause, prevention, and methods of diagnosis and treatment of cancer.

(b) Promote the coordination of researches conducted by the Institute and similar researches conducted by other agencies, organizations, and individuals.

(c) Procure, use, and lend radium.

(d) Provide training and instruction in technical matters relating to the diagnosis and treatment of cancer.

(e) Provide fellowships in the Institute from funds appropriated or donated for such purpose.

(f) Secure for the Institute consultation services and advice of cancer experts from the United States and abroad.

(g) Cooperate with State health agencies in the prevention, control, and eradication of cancer.

To insure a broad research attack on the cancer problem from every

disciplinary approach, the Act also authorized grants of funds to support the research of scientists in other institutions and established the National Advisory Cancer Council to review applications and recommend awards of grants to be made by the Surgeon General.

Briefly, the authority of the Advisory Council included the following:

(a) Review of research projects or programs submitted to it by others or initiated by its own members, and recommendation to the Surgeon General of any considered worthy of prosecution under terms of the Act.

(b) Collection of data regarding studies carried on in this country or elsewhere relative to cancer, and dissemination of this information through appropriate publications.

(c) Review of applications for grants-in-aid for cancer research projects and certification to the Surgeon General of its approval of those showing promise of making valuable contributions to knowledge of cancer.

(d) Recommendation of acceptance of conditional gifts offered to the Institute for cancer work.

The six members of the Advisory Council were to be selected from leading medical or scientific authorities who were outstanding in the study, diagnosis, or treatment of cancer in the United States. New legislation enacted in 1950 increased the membership of the Council to 12, including lay leaders in fields of public affairs.

Organization Period

The first appropriation for the National Cancer Institute was a modest $400,000, half of which was earmarked for the purchase of radium. The members of the National Advisory Council were appointed soon after approval of the Act, and the Council held its first meeting on November 9, 1937. A small administrative staff was assembled by Dr. L. R. Thompson, Director of the National Institute of Health, as the research arm of the Public Health Service was then called. Dr. Carl Voegtlin was appointed first Director of the Institute. Work was then in progress on the erection of five buildings comprising the first structural units of the present National Institutes of Health at Bethesda, Maryland on a tract of land donated by Mr. and Mrs. Luke L. Wilson. Mrs. Wilson, whose husband died after the original gift was made, donated an additional tract of land as the site of a building for the National Cancer Institute.

The various types of activities authorized by the National Cancer Institute Act were gradually put into operation. During the first year the Advisory Council recommended approval of ten research grant applications totaling $91,000. One of the first grants was made to support the work of Dr. E. O. Lawrence at the University of California in developing the cyclotron for clinical research on therapeutic uses of neutron rays and artificial radioactive substances.

The first research fellows were appointed in 1938, some of whom worked at the National Cancer Institute and others on grant-supported research

projects. A program of clinical traineeships was also inaugurated for young physicians who, having completed at least a full year of internship, could apply for training in cancer diagnosis and treatment offered at approved centers. The traineeship program was in operation by June 30, 1938 with 14 young doctors enrolled.

Because of the numerous technical details involved, the radium loan program could not be activated until the fall of 1939. The Institute purchased 9½ grams of radium in 1,600 units ranging from 1 to 25 milligrams and about 1 gram in solution to be used in a radon plant. During the year required for testing the radium at the U. S. Bureau of Standards details for shipping the material, standards required of borrowing institutions for the protection of their personnel, and standards for training of radiologists using government radium in treating patients, were worked out. By July 1940, loans had been made to 47 hospitals.

For the conduct of research in its own laboratories, the new Institute had as the nucleus of its scientific staff a group of investigators who had been conducting cancer research in the Public Health Service for 15 years. This work had been done by two independent groups, one housed at Harvard University and the other at the Hygienic Laboratory in Washington, D. C. The original intramural staff of about 10 scientists was augmented by fellows, many of whom later became regular employees of the Institute.

Development of a clinical cancer research center was undertaken at the U. S. Marine Hospital in Baltimore, with a new 100-bed addition to the

hospital. Although World War II prevented realization of its full potential, this unit provided facilities for a considerable program before the opening of the Clinical Center at the National Institutes of Health in 1953.

In the organization period the first steps were also taken toward a cancer control program by providing funds to the States Relations Division of the Public Health Service for studies of cancer mortality and epidemiology.

Development of Programs

The onset of World War II necessitated serious modification of program development following establishment of the Institute's organizational pattern. The possibility that the United States would become actively involved in the war, which was definite by 1940, dictated curtailment of long-term research projects on which money and effort would be wasted in the event the work could not be completed. When this country was attacked in 1941, the main problem for the Institute became the loss of personnel who either entered military service or resigned to go into work directly connected with the war effort. Cancer work continued at much reduced scale, but planning for postwar research and related activities was continued during the war period.

Despite the inhibitions placed upon the Institute's development by the war emergency, several important contributions to the advancement of research were made in this critical period in addition to such direct

laboratory efforts as the outstanding early research on nutrition and enzyme aspects of cancer. One of the greatest needs of the time was increased publication outlet for scientific papers in the field, since there was then only one professional journal devoted wholly to cancer research. The Journal of the National Cancer Institute was established in 1940 as a bimonthly publication. Epidemiological studies were advanced with a survey of cancer morbidity in ten selected metropolitan areas, and the work formed the basis of a second survey ten years later which produced comparative data. A survey of compounds tested for carcinogenic activity was published in 1941, and staff scientists conducted an important symposium on tumors in mice which was published in 1945.

Postwar resumption of full-scale activities was signalled by an appropriation of $14,500,000 to the Institute for the fiscal year 1948 compared to $1,800,000 for 1947. The demonstrated success during the war of large scale research efforts for solving problems of importance to society led to this initiation of the new era of larger governmental support of research. From that time forward the annual appropriations were steadily increased, and research and control programs were correspondingly enlarged and diversified. New activities included promotion of nurse education in cancer, and a public information service in response to increasing demand for reports and announcements on the status and progress of cancer research and related efforts.

Beginning with the first large appropriation for 1948, a major

proportion--75 to 80 per cent-- of the Institute's funds has been allocated to grant support of research, and to fellowships and other types of training. Grants have been made for specific research projects in universities and other research institutions and for comprehensive research programs developed by such institutions. Fellowships have been awarded to individuals working in recognized research institutions and stipends to physicians preparing to specialize in cancer diagnosis and therapy. Grants for cancer training in medical, dental and osteopathic schools have been awarded annually. Active participation by large numbers of investigators widely drawn from the scientific community through their service on numerous advisory groups has not only insured wide acceptance of these programs, but has also allowed broad application of many outstanding and diverse talents to the selection of projects for grant support.

Cancer control activities were developed largely in the areas of financial support for State programs, physician and nurse training, field investigations, community studies, surveys and pilot projects in diagnostic and case-finding techniques. One of the outstanding projects of this type was the establishment of studies in Memphis, Tennessee and several other localities in different parts of the country to test the reliability of the cell examination procedure as a case-finding device and aid to diagnosis in uterine cancer. Largely through this kind of effort the "Pap" smear is receiving increased medical and public acceptance and is credited with a substantial reduction in uterine cancer mortality.

With the opening of the Clinical Center of the National Institutes of Health in 1953, the Institute was able to inaugurate a full-scale clinical research program, with approximately 140 beds now available for studies in which cancer patients participate. Non-clinical research programs continued to be developed in the major fields of cancer investigation, organized under laboratories representing such scientific disciplines as biology, biochemistry, biophysics, pathology, etc.

The importance of scientific publication as a part of research has remained a foremost consideration in the development of the Institute's activities. The Journal of the National Cancer Institute, enlarged and diversified with the inclusion of many papers by scientists not of the Institute's staff, became a monthly publication in 1956. It also provides the aegis for a series of National Cancer Institute Monographs for the publication of proceedings of scientific meetings of wide interest and long reports of major studies in different fields of cancer research.

A trend toward the large-scale coordinated research approach in selected areas began with the establishment of a national, voluntary cooperative cancer chemotherapy program in 1955. This activity had its genesis in a request by Congress in 1953 that the Institute explore the feasibility of an engineered, directed extramural research program in the chemotherapy of acute leukemia. With the establishment of the Cancer Chemotherapy National Service Center in the National Cancer Institute two years later, the integrated program was expanded to an annual level of

approximately $30 million for the testing of hundreds of thousands of compounds through preliminary screening in animals, pharmacological study, and evaluation of promising drugs in many forms of human cancer.

Several other areas were selected more recently for this type of exploitation. In one, carcinogenesis, a large-scale integrated program of direct operation utilizing a contract mechanism to supplement intramural staff and facilities had been set in motion for an exhaustive study of environmental and other factors bearing on the causation and prevention of cancer. In another area a task force is making intensive joint effort to elucidate the role of viruses as a possible cause of human cancer. In still another, a task force is concentrating efforts on intensive application of several new treatment techniques in the attempt to find better ways to help--and hopefully to cure--the acute leukemia patient.

The programs of research and training inaugurated 25 years ago under a modest budget of $400,000 now operate at a level of nearly $150 million. Cancer control was recently turned over wholly to the Bureau of State Services under a reorganization of the Public Health Service. Diverse sound cancer research approaches conceived and conducted by investigators in universities and other research organizations in this country and in special cases abroad are widely supported by approximately 2,000 grants currently in effect. Direct operations include the management of broad-scale, integrated multiple-discipline, cooperative nation-wide

programs financed mainly through contracts, and intramural research under program planning that has been developed with the aid of review committees and a Scientific Directorate composed of top-level staff scientists and administrators. The range and scope of the numerous activities supported by these funds is very extensive since cancer is a term applied to a large collection of diseases, and modern cancer research involves nearly all the scientific disciplines in the biomedical sciences and many in the physical sciences as well.

The Research Objective

The National Cancer Institute was established to expand and intensify research on one of the most formidable problems in the history of medical science. Reports of progress against the disease seem to present a paradox. In 1935, when efforts on behalf of legislation to create the Institute were nearing success, the death rate from cancer was 108 per 100,000 population. In 1940 the rate was 120, and in the next ten years it rose to 140. By 1960 it stood at 148. On the other hand, in the mid-thirties fewer than one in five cancer patients recovered, whereas today one in three are saved. And with full doctor-patient cooperation in the optimum situation probably one in two could be saved.

The Threat of Cancer

The threat of cancer remains serious. In the United States, there will be 530,000 new cases diagnosed in 1963, and a total of 815,000 cancer patients will be under medical care during the year. There will be 280,000 cancer deaths (one cancer death every two minutes), a total exceeded only by deaths from cardio-vascular diseases.

This year, however, 177,000 cancer patients will be saved by medical treatment. They will join the ranks of 1,200,000 former cancer patients who are considered cured in the sense that they have lived at lease five years without evidence of disease.

But if present rates continue, 46 million Americans now living will eventually have cancer. This reliable statistical projection, and the

fact that at least 50 per cent of cancer victims are still without hope of recovering, express the demand for continued vigorous research to conquer the nation's second largest killer.

Role of the National Cancer Institute

The magnitude of the cancer problem left no doubt in the minds of many who viewed it in 1937 that an adequate research attack could hardly be mounted with the resources of private philanthropy or industry alone. It was clear that only participation and leadership by the Federal Government could make possible the full mobilization of financial and scientific resources necessary to meet the challenge.

Initially, the need in research was to increase scientific knowledge concerning any and all biological, chemical and physiological phenomena that might be involved in the cancerous process. This kind of detailed, methodical investigation was pursued by scientists of virtually every discipline related to biomedical research, and a great deal of what has been learned remains largely unknown to the public in terms of direct applied results. It is vital, however, to research development and constitutes the indispensable foundation for future advances, some of which have already been of direct benefit to cancer patients.

Over the years the basic research findings have provided a base of knowledge that will now permit investigation of areas of particular promise which should be vigorously pursued by a coordinated, interdisciplinary research approach. Institute programs have therefore increased in size, scope and complexity, requiring the integration of

various operations and the planning of future activities within the context of a long-range, total program of cancer research.

Today the National Cancer Institute supports the great majority of research on cancer in the United States and a portion of that conducted in other countries. It does this by the work of its own scientific staff, by grants, and by contracts. The results are so inextricably interwoven into the total fabric of scientific knowledge about cancer that it is impossible to define precisely the boundaries of the Institute's contribution. It can be said with assurance that this contribution has been vital.

The administration of these cancer programs as the focal point in a national setting requires an uncommon blending of scientific and administrative skills difficult to find, particularly in an area with such broad scope and complexity as cancer research. The organization of the National Cancer Institute brings together in one place those who both conduct research and administer these broad, nation-wide programs, to form a unique device for carrying out such an activity. The research is continually evaluated not only by staff, but by the Nation's top scientific leaders from universities, hospitals, research institutes, and other organizations. This sizeable volume of research has been judged to be of a high order of excellence, and it is increasingly involved directly and indirectly with most of the advances being made against cancer.

As previously emphasized, cancer has been one of the most formidable

problems in the history of medical science, and much remains to be done. Behind all these efforts is the cancer patient refractory to radiation and inaccessible to surgery for whom something more must be done. The Congress showed great foresight in creating as the focal point of a national effort the National Cancer Institute, and steady progress against the threat of cancer has been made. The degree of success in the future will continue to depend, to a great extent, on both the level and type of support made available for this work.

Organization

The present organization of the National Cancer Institute reflects both the long-range mission of the Institute as formulated by Congress and the current status of cancer research as evidenced by broad areas of greatest activity.

The Director of the National Cancer Institute, appointed by the Surgeon General of the Public Health Service, is responsible for all cancer research activities of the Service. In addition, he gives technical guidance and assistance to the Cancer Control Program of the Bureau of State Services, and he and his staff cooperate with other Federal agencies and voluntary organizations in the cancer field.

Senior Management Staff

In discharging his responsibilities, the Director relies heavily on his senior management staff consisting of: an Associate Director for Program who works closely with the Director in planning, analyzing, and coordinating major Institute programs; an Associate Director for Grants and Training; an Associate Director for Field Studies who is responsible for nation-wide, multi-disciplinary programs of research on cancer causation and prevention and for the assemblage of information on cancer incidence, mortality, results of treatment, geographic distribution, and the like; an Associate Director for Collaborative Research who is responsible for managing nation-wide, cooperative research programs in chemotherapy, virology research resources, and diagnosis; and a Director of Intramural Research who has responsibility for conducting both clinical and nonclinical investigations.

The Director's staff also includes the Executive Officer, Assistant Director, and Special Assistant for liaison with international activities.

Scientific Directorate

The senior management staff and others responsible for major program segments comprise a Scientific Directorate to advise the Director on research and related programs, coordinate operations, and give final review to contract proposals for investigations requiring personnel and facilities beyond those existing in the Institute. Its consultative services are available also to the staff of any organizational segment of the National Cancer Institute program.

Key members of the Institute scientific staff have recently been organized as standing committees under the Scientific Directorate. In addition to advising on the development and implementation of research programs on cancer causation and prevention and on diagnosis and treatment, these committees are performing preliminary screening of contract proposals. Outside consultants are called on to assist the staff in reviewing contracts on an ad hoc basis.

Research areas of high import are the concern of two task forces whose memberships include prominent investigators from other institutions as well as Institute staff. These task forces have been assembled to conduct intensive investigation, over a limited period, of acute leukemia therapy and of viruses as a possible cause of human cancer.

Advisory Bodies

Two major advisory bodies assist in reviewing and planning the Institute program: the National Advisory Cancer Council and the Board of Scientific Counselors.

The National Advisory Cancer Council is a body of 12 appointive members and three ex-officio members created by law to advise the Surgeon General on general policies, programs, and needs, and, specifically, to review and recommend appropriate action on applications for grants-in-aid for research, and for training related to research on the cancer problem. The Council meets regularly three times a year. Its two subcommittees focus on the same general areas as do the standing committees of the Institute staff: carcinogenesis and prevention; diagnosis and treatment.

Of the 12 appointive members of the Council, not less than half must be scientists or physicians, skilled and experienced in the problems of cancer. Other members may be educators, research administrators, or other lay leaders in fields of public affairs.

Giving review to all aspects of the intramural program of the Institute is the Board of Scientific Counselors. Twice a year this six-member Board of non-governmental scientists meets with key members of the Institute scientific staff to discuss selected research and organizational problems.

Personnel

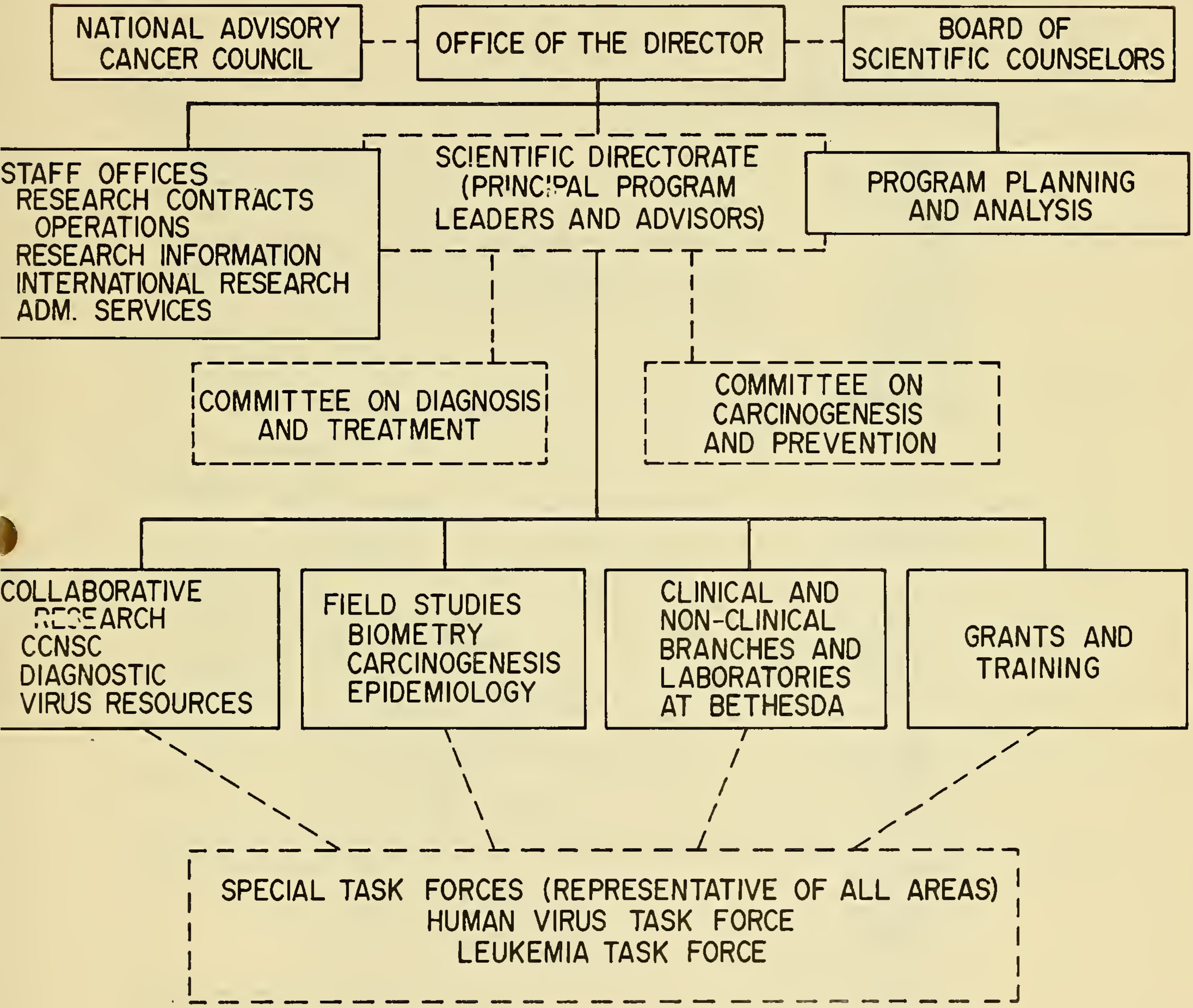
As of March 1963 a total of 1,224 persons were on duty at the National Cancer Institute. The professional, scientific and technical staff numbers

516, of whom 275 hold doctoral degrees in medicine or one of the other scientific disciplines.

The organization of the National Cancer Institute is shown on the accompanying chart.

NATIONAL CANCER INSTITUTE

ORGANIZATIONAL AND FUNCTIONAL PROGRAM


NATIONAL ADVISORY CANCER COUNCIL
OFFICE OF THE DIRECTOR
BOARD OF SCIENTIFIC COUNSELORS
STAFF OFFICES
RESEARCH CONTRACTS OPERATIONS
RESEARCH INFORMATION
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ADM. SERVICES
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COLLABORATIVE RESEARCH
CCNSC
DIAGNOSTIC
VIRUS RESOURCES
FIELD STUDIES
BIOMETRY
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EPIDEMIOLOGY
CLINICAL AND NON-CLINICAL BRANCHES AND LABORATORIES AT BETHESDA
GRANTS AND TRAINING
SPECIAL TASK FORCES (REPRESENTATIVE OF ALL AREAS)
HUMAN VIRUS TASK FORCE
LEUKEMIA TASK FORCE

TABLE 1
BUDGET SUMMARY
NATIONAL CANCER INSTITUTE
(In Thousands of Dollars)

	1963 Apportionment
GRANTS	
Research	
Regular program	$ 47,163
Programmed chemotherapy	4,300
Additional indirect cost	746
Categorical clinical research centers	4,833
Scientific planning evaluation	146
General research support grants	4,100
Total	61,288
Fellowships	4,788
Training	11,470
Total Grants	77,546
DIRECT OPERATIONS	
Research - NCI	8,186
Mgmt. Fund	7,911
Total	16,097
Collaborative Studies	
Field studies	3,560
C.C.N.S.C.	1,638
Chemotherapy contracts	26,914
Virus activities	6,096
Diagnostic research activities	2,647
Ghana Research Laboratory	650
Total Collaborative Studies	41,505
Review & Approval - NCI	798
Mgmt. Fund	971
Total	1,769
Program Direction - NCI	464
Mgmt. Fund	621
Total	1,085
Total Direct Operations	60,456
Comparative transfer to BSS	10,202
Unprogrammed reserve	7,538
Total Appropriation	$155,742

Table 2
NATIONAL CANCER INSTITUTE
RESEARCH GRANTS PROGRAM
DISTRIBUTION BY MAJOR SCIENCE FIELDS
FISCAL YEAR 1962

			Number of Projects	Dollar Amounts
Biochemistry:			797	$ 21,315,457
Amino Acids and Peptides	16	$ 274,024		
Intermediary Metabolism	49	1,161,548		
Carbohydrates	6	139,869		
Enzymes	101	2,596,905		
Fatty Acids and Lipids	12	194,586		
Growth Inhibition or Regression	316	9,277,551		
Hormones and Steriods	153	3,936,983		
Nuclear Proteins and Components	75	2,254,286		
Other Proteins	45	967,056		
Organic Radicals	4	57,300		
Vitamins and Nutrition	20	455,349		
Biophysics			12	251,142
Chemistry (other than bioch.)			79	1,330,673
Genetics			52	1,253,346
Histology and Cytology			130	2,627,495
Immunology			65	1,487,800
Microbiology			5	113,028
Morphology			229	5,132,982
Physiology (Primary Metabolism)			108	2,421,250
Radiology			93	1,768,480
Surgery			17	263,800
Virology			106	4,011,221
Other			45	2,063,989
Sub-Total			1738	$ 44,040,663
Multiple Discipline Program Projects			8	3,566,484
TOTAL			1746	$ 47,607,147

Table 3
NATIONAL CANCER INSTITUTE
RESEARCH GRANTS PROGRAM
DISTRIBUTION BY MAJOR CANCER RESEARCH AREAS
FISCAL YEAR 1963

			Number of Projects	Dollar Amounts
Cancer Causation			357	$ 8,541,201
Cancer Morphology and Physiology			260	6,485,474
Host-Cancer Relations			86	2,116,502
Cancer Diagnosis			84	1,465,113
Cancer Epidemiology			31	727,755
Treatment of Cancer:			574	15,651,100
Cooperative Clinical Trials	147	$5,272,687		
Other Chemotherapy	377	8,896,077		
Other Treatment	50	1,482,336		
Basic Research			346	9,053,518
Morphogenesis				
External Stimuli	13	275,253		
Internal Stimuli	48	947,749		
Differentiation & Growth	51	1,102,655		
Steady State Morphology & Physiology	156	4,315,805		
Integrative & Immune Physiology	40	1,029,115		
Other	38	1,382,941		
Cancer "Centers and Program Projects"			8	3,566,484
Total			1746	$47,607,147

National Cancer Institute Programs

Introduction

From the historical standpoint, modern cancer research began in the middle of the last century. The flowering of microscopic pathology at that time led to a classification of tumors and cancerous diseases based predominantly on morphological characteristics as seen through the microscope. As is usually their privilege, the taxonomists who studied cancer structure created the terminology of the classification, and this terminology persists today. Much of the current conceptual thinking about cancer has been directed by immersion in this terminology and classification, and considerable effort needs to be expended to develop new conceptual frameworks on entirely different classification schemes than those derived from this century old classification.

Following the initial descriptive period, tumor transplantation techniques were evolved, inbred animals were developed, and the beginnings of an understanding of the relationships of cancer and genetics were established. Much experimental work over the first half of this century was concerned with detecting qualitative differences among the morphologically different types by measures other than morphology (e.g., chemical differences), but this qualitative difference for the most part has not been found. However, striking quantitative differences are now known which have important implications, especially for

approaches to therapy; over this same period, investigators were seeking likenesses, mainly chemical ones, among different morphological types of tumors, and, although transplanted tumors show similarities such as enzyme activity patterns, the similarity, if it exists, has not yet been demonstrated for spontaneous tumors. Moreover, throughout this period of the past 150 years, it was commonly assumed that tumors of one morphological type contained cells that were alike. The past decade has produced evidence that makes such a view no longer tenable, since it is now known that tumors consist of a mosaic of cell types with different characteristics and properties, and, as cell divisions occur during tumor growth, new cell types appear. This changing composite provides a difficult subject of study and accounts for many difficulties encountered in diagnosis and treatment of cancer.

A considerable body of epidemiologic data implicating coal tars, soot, and certain mineral oils in the induction of skin cancer in occupational groups working with these substances was at hand by the turn of the century, and extensive investigational work was undertaken during the next four decades to identify the precise components in the environment responsible for cancer initiation; by 1915 the experimental induction of cancer by means of exposure to radiation, viruses or chemical substances was accomplished; the next year saw the demonstration of the influence of hormonal factors on the development of breast cancer; during the twenties and thirties several hydrocarbons were identified as powerful carcinogenic agents in experimental animals;

today more than 450 compounds have been shown to induce cancer in experimental animals and some have been implicated in human cancer causation.

Over the past two decades many important aspects of cancer induction have been elucidated:

1. Dose response curves for cancer induction have been determined for ionizing radiation and for chemical substances.

2. Many species differences in response to agents have been determined.

3. The types of substances vary from such inert materials as platinum to highly potent compounds, such as 1,2:5,6-dibenzanthracene, active in the microgram dose range.

4. Classes of chemical compounds range from inorganic to several types of organic compounds (more than 200 of the 450 known agents are polycyclic hydrocarbons; more than 50 are azo dyes; and a substantial number are aromatic amines and carbamates).

5. The importance of routes of administration (by feeding, inhalation, skin, contact, subcutaneous or intramuscular injection) has been established.

6. Statistical techniques required for relating the experimental group to the control groups have been greatly advanced.

7. Epidemiologic techniques have not only established important demographic data, but have also uncovered new leads that call for more intensive investigation.

In the past 15 years some of the additional cancer research accomplishments include the following:

1. One form of cancer (choriocarcinoma) in women has been successfully treated with drugs alone.

2. The use of the Papanicolaou vaginal smear test has reduced mortality from uterine cancer.

3. Advances in drug treatment and supportive therapy have resulted in a fourfold increase in the median survival time of children who have acute leukemia.

4. Platelet and granulocyte transfusion techniques were introduced which reduce the risk of fatal hemorrhage and infection in acute leukemia patients.

5. An enzyme procedure (LDH determination in dialyzed urine specimens) has been developed for detection of kidney and bladder cancers.

6. A new hormone (2-alpha-methyl-dihydrotestosterone propionate) useful in treatment of breast cancer and producing fewer side reactions was introduced.

7. Advances were made in treatment of chronic leukemias, especially with chlorambucil.

8. Drug treatment (ThioTEPA) has reduced the frequency of recurrence among women who underwent surgery for breast cancer.

9. An isolation-perfusion technique was developed that makes it possible to achieve higher concentrations of anticancer drugs at the site of tumors than can be given by conventional means.

10. Screening and end-results techniques for evaluation of drugs were greatly improved.

11. Cigarette smoking was linked statistically to the increased incidence of lung cancer.

12. A virus (polyoma) that causes multiple tumors in animals of various species was isolated and grown in tissue culture.

13. Viruses were established as a cause of leukemia in mice.

14. Virus particles were found in the blood of experimental animals and man with leukemia.

15. Tumor-inducing nucleic acids were isolated.

16. Animals were successfully immunized against the development of some types of virus-induced tumors.

17. Human viruses (adenovirus types 12 and 18) were shown to cause tumors in animals.

18. An animal virus (SV 40) was found to cause abnormalities in human cells growing in tissue culture.

19. Experiments with animals indicated that viruses (influenza) and chemicals (ozonized gasoline hydrocarbon fractions) can interact to cause cancer.

20. Some industrial cancer hazards (e.g., chromium ore fractions) were identified and controlled.

It is most probable that successes in treatment, diagnosis, and prevention will continue to occur by small increments, probably for the most part in individual clinical types of cancer, rather than as single major breakthroughs applicable to all types of cancer.

Additional description of Institute programs are given below, and, in the space available, only a few examples of research progress can be given.

Intramural Program

The intramural research program is conducted by investigators devoting their full time efforts to cancer research, in the NIH setting where other full time investigators, both clinical and non-clinical, expert in the various fields of modern biomedical research are available for mutual stimulation, sharing of knowledge, and collaboration on research problems. It includes major approaches seeking to learn the causes of cancer and ways it may be prevented, to find increasingly better ways of diagnosing the disease in its earliest stages, and to treat it effectively. The large-scale combination of clinical programs (supported by outstanding clinical laboratory back-up) and the basic research programs provides unusual research opportunities, particularly in the clinical chemotherapy research area.

Laboratories and Branches

Numerous research projects are conducted in basic independent and interdependent disciplines, and many of them cut across clinical and non-clinical lines. In the laboratory and clinic, the production of knowledge is continuously in a state of dynamic equilibrium, the exploratory basic research findings nourishing the clinical studies, which in turn provide new knowledge and new facets for fundamental research.

The Laboratories of Biochemistry, Biology, Chemical Pharmacology, Physiology, Pathology, and Viral Oncology are non-clinical, basic-science departments; the Dermatology, Endocrinology, Medicine, Radiation, Surgery, and Pathologic Anatomy Branches, and the Metabolism Service are clinical departments of the intramural program.

Basic-science investigations are concerned with studies of the cancer-causing effects of viruses, chemicals, and radiation and with attempts to understand the neoplastic transformation in chemical and molecular terms. Special interest has focused, for example, on the role of viruses alone and in combination with environmental factors, such as chemicals in the atmosphere, on the susceptibility of newborn mammals to carcinogenic influences, and on the interrelationship of specific cancer-causing substances and components of the cell, particularly nucleic acids.

The influence of the host on the development of cancer is studied in investigations of genetic factors, hormonal environment, immunologic status of the host, and other nonspecific factors of metabolic or cellular origin. Conversely, the growing tumor has an impact on the host; and the physiological and chemical properties of the tumor are investigated, as well as environmental factors as they relate to tumors.

Clinical studies extend the findings of previous experience with the disease and utilize knowledge gained through research carried out

in the basic-science laboratories. The principal clinical studies include the evaluation of various drugs in the management of neoplastic diseases, the role of endocrine glands in hormone-dependent and hormone-sensitive tumors, evaluation of radical surgery in cancer of the uterus, and work on dose and dose rate in radiation therapy. In addition to studies of therapy, the clinical branches investigate the natural history of various types of neoplastic disease and carry out biochemical and physiological studies of the effect of the tumor on the individual.

Recent Program Developments

The diverse and versatile skills of the scientists of the intramural program have contributed importantly to the productivity of approximately a quarter of a century of intensive cancer research in this country. In years past, the main emphasis was on experimental research in the laboratory to study cancer in animals and develop new equipment and techniques of refinement and specialization. These studies were intended primarily to gain knowledge of how cancer originates, how it progresses, and how it affects the organism it attacks. In the last ten to fifteen years, however, the study of cancer in man has become both more urgent and more promising. It has become more urgent as findings in the laboratory became more suggestive of profitable approaches to the human problem. It has become more rewarding and promising as these approaches began to yield

results that benefit cancer patients and could be used as a basis for more penetrating studies.

The requirements of research programs for intensive investigations of the causation, diagnosis, and treatment of human cancer are beyond the physical resources of any one institution. The National Cancer Institute has taken the lead in organizing new approaches which are designed to overcome some of these limitations and thereby avoid a lag in the progress of this research.

One of these approaches extends the Institutes's intramural activities and other direct operations by means of contracts with independent research laboratories or institutes to conduct investigations requiring personnel and facilities in excess of those normally available. The contract mechanism also provides materials and resources needed by cancer investigators throughout the country who are being encouraged to pursue promising lines of research such as viruses in relation to cancer and environmental and other cancer-causing factors. The contract procedure originated in the Institute's chemotherapy program for the development of effective cancer drugs and has been extended to the virus, diagnostic, and field studies research activities.

An approach devised within the past year resulted from an obvious need for focusing the efforts and resources of groups of investigators

in two highly promising research areas. Accordingly, two task forces have been established under Institute auspices.

The Human Cancer Virus Task Force under the chairmanship of the Chief of the Institute's Laboratory of Viral Oncology is composed of scientists representing four laboratories of the National Cancer Institute, three non-Federal institutions, and one laboratory of the National Institute of Allergy and Infectious Diseases. The Task Force is an informal working group which will explore selected avenues through which the role of viruses in the induction of human cancer may be elucidated. Its objective is to obtain answers to important specific research questions within a limited period of time, at the end of which decisions will be made on the future direction of the virus-cancer research effort. As a beginning, high priority is being given to the leukemias and lymphomas because of the nature of the diseases and because of the knowledge available from animal model systems. Preliminary plans have been made to search for human counterparts to animal leukemia viruses and to screen large populations of apparently normal individuals and cancer patients for evidence of their exposure to viruses that might be linked to development of malignancies.

The second group is the Acute Leukemia Task Force organized under the chairmanship of the Institute's Scientific Director. It includes Institute staff members as well as prominent investigators from

several other institutions participating in the leukemia studies conducted under the auspices of the collaborative chemotherapy program administered by the Institute. The objective of this task force is to focus closely coordinated efforts and resources on intensive chemotherapeutic and supportive treatment of the acute leukemia patient.

Research Progress

The National Cancer Institute's intramural staff have contributed substantially to the research accomplishments which have brought into prominence the two areas currently under intensive investigation--viruses as possible causes of human cancer and treatment for acute leukemia patients. Equally vital information and laboratory techniques have been produced in many other areas of the cancer problem which will no doubt provide the background for future intensive research efforts. A few illustrations will indicate the scope and variety of the Institute's intramural accomplishments.

Events of the past decade have pointed to viruses as particularly likely suspects for at least some types of cancer. One of the findings that gave a strong impetus to cancer virology research was the observation by Dr. Sarah E. Stewart of the National Cancer Institute that a virus-containing cell-free extract, which was reported by another scientist to produce leukemia in newborn mice, caused salivary gland tumors to develop. In collaboration with

Dr. Bernice E. Eddy of the Division of Biologics Standards, National Institutes of Health, Dr. Stewart was able to grow large amounts of virus in cultures of mouse embryo tissue by inoculating the tissue cultures with cell-free tumor extracts. By this means they demonstrated that the original cell-free extract contained both a leukemia virus and a salivary gland tumor virus. The biological activity of the salivary gland tumor virus (called polyoma virus) was increased in tissue culture so that it not only produced more than 20 different kinds of tumors in mice, but even crossed species barriers to cause tumors in rats and hamsters.

Dr. Stewart demonstrated the possibility that vaccination might some day prevent some cancers in man, when she found that mice did not develop tumors when inoculated with a mixture of polyoma virus and serum containing antibodies to the virus, or when given separate but simultaneous inoculations of virus and antiserum.

The discovery of virus particles in the blood of leukemia-bearing animals by Dr. John B. Moloney in collaboration with Dr. Albert J. Dalton, both of the National Cancer Institute, provides an exceptionally useful prototype for the development of approaches to human virus-leukemia studies. The virus producing this type of leukemia was discovered by Dr. Moloney, and he and Dr. Dalton worked out a method of recovering the virus in essentially pure form by spinning the blood at high speeds in a centrifuge. The pellet thus

produced is studied with the electron microscope.

Research on viruses as a possible cause of human cancer continues with the use of tissue culture for exploration of their role in malignant change. Under the leadership of Dr. Wilton R. Earle, tissue culture has been a major area of research in the National Cancer Institute from its establishment nearly 26 years ago. Dr. Earle has pioneered many developments in tissue culture, several of which formed the foundation for many advances dependent upon tissue culture techniques, including the important successes in the poliomyelitis areas, and now in cancer virology. Dr. Earle and his co-workers developed large-scale cultures of cells, which have become essential in such operations as vaccine production. This team also formulated an entirely chemically defined medium that supports cell growth without the addition of human or animal serum, thus eliminating the possibility of contamination by viruses or other extraneous material, and providing a highly controlled environment for study of normal and cancer cells. This group also demonstrated that change from the normal to the malignant state occurs in cells grown in tissue culture and that progeny produced from single cells show divergent properties in long term tissue culture, including cancer development.

In the second area in which great interest is focused, chemotherapy, Institute intramural scientists have also played a leading role. For the first time, a high proportion of cancer

patients of any one type have been freed of the disease (as evidenced by a highly sensitive hormonal test) through the use of drugs alone, and several of these patients have now lived for more than five years with no indication of cancer. This accomplishment was achieved by Dr. Roy Hertz, Chief of the Institute's Endocrinology Branch, and his co-workers. The type of cancer is choriocarcinoma, a highly malignant tumor sometimes arising in the uterus during or following pregnancy, and the drug is methotrexate. Dr. Hertz and his colleagues have also shown that two other drugs, actinomycin D, an antibiotic, and Vinblastine, a plant extract, are useful in treating patients in whom the disease has become resistant to methotrexate.

Research in acute leukemia, the focus of one of the two task forces, is of the highest importance to Institute clinical investigators and has produced some of their most gratifying accomplishments. Some of this work is described elsewhere in this report under "Collaborative Research Programs."

National Cancer Institute scientists have been responsible for many important fundamental scientific observations related to the cancer problem. The biophysicist, the late Dr. Egon Lorenz, discovered that mice exposed to a lethal dose of x-radiation could be protected by injection of bone marrow from mice of the same strain. He and his colleagues also found that marrow from other strains and even from other species was protective, though to a lesser extent.

Dr. Howard B. Andervont, former Chief of the Laboratory of Biology and now Scientific Editor of the Journal of the National Cancer Institute, has made many basic contributions to biomedical research relating to viruses, polycyclic hydrocarbons, hormones, and heredity. He contributed importantly in studies demonstrating conversion of strains of mice in which breast cancers occurred infrequently to those with a high incidence of such tumors by foster-nursing the animals with milk containing the mouse mammary virus. In studies of chemical carcinogenesis, he showed that the nature and duration of the cancer-inducing stimulus influenced the biological properties of the cancer, such as length of time before appearance of a tumor and size of the tumor. A steady output of other basic research contributions continue from the staff in such areas as biochemistry, genetics, pharmacology, immunology, and so on.

Extramural Program

Under the direction of the Associate Director for Grants and Training, the extramural program is responsible for the planning, development, and execution of grant and award programs for support of cancer research and training throughout the United States and in some foreign countries. This is the largest of the Institute's programs, and it encompasses not only research projects in a broad spectrum of clinical and basic science fields, but also special training of scientists and physicians, and construction of certain cancer research facilities.

Research Grants

The National Cancer Institute administers three related types of Public Health Service research grants for the support of cancer investigations in research hospitals, universities, and other institutions. The research project grant is an award to an institution for the support of research by one or more investigators on a problem that is generally limited in scope and in the time required to solve it. When such projects combine several different types of approach and the use of several different disciplinary methods of conception and execution by a team of investigators, they may be termed program-project or clinical research center grants.

In addition to the support of research in cancer chemotherapy conducted by independent investigators by regular research project grants, Programmed Chemotherapy grants are awarded to support the

research of individual investigators who participate in the cooperative group evaluation of drugs in clinical trials according to protocols of the Institute's Cancer Chemotherapy National Service Center (see below under Collaborative Research).

The Institute provides a substantial sum as its share in the maintenance of the General Research Support Program of the National Institute of General Medical Sciences. The purpose of the institutional grants made under this program is to provide funds for the general support of medical research and research training programs designed to meet needs not adequately met by categorical modes of support.

Grants are awarded only after thorough review and recommendation by the National Advisory Cancer Council. The Council is aided by special consultant advisory groups, including the Clinical Studies Panel of the Cancer Chemotherapy National Service Center and a great many of the Study Sections of the Division of Research Grants of the National Institutes of Health.

The Research Grants Branch is responsible for seeing that adequate preliminary review is given all cancer research project grant applications, for presenting them to the National Advisory Cancer Council for recommendation, and for the administration of all research project grants that are awarded. This Branch participates in the policy planning and administrative decisions that concern research

project grants. The Branch develops and carries out studies of the needs and opportunities for special emphasis in cancer research for consideration by the National Advisory Cancer Council and the Institute's Director, and participates in the stimulation and development of special support programs that may be instituted to meet the needs or exploit the opportunities.

In fiscal year 1962, grants were awarded for 1,738 research projects and 8 multiple discipline program projects, making a total of 1746 projects.(Table 2.) The awards made in support of investigations of cancer treatment, numbering 574, constituted the largest share of the total number of projects. Awards on cancer causation, basic research, and cancer morphology and physiology numbered 357, 346, and 260, respectively. (Table 3.)

The scientific advances made over the years by research workers supported by Institute grants have been significant in all areas of the cancer problem. For example, in research on viruses as a cause of cancer, an area in which the Institute has focused intensive efforts, more than 190 grants are in effect in this country and abroad. Dr. Charlotte Friend, a grantee at the Memorial Sloan-Kettering Cancer Center, discovered a virus that causes a type of leukemia in mice and went on to develop a killed-virus vaccine that protects mice against the disease.

A vaccine that reduces the frequency with which virus-caused

benign tumors in rabbits become malignant was developed by Drs. Yohei Ito and Charles A. Evans, Institute grantees at the University of Washington. These investigators also demonstrated that the nucleic acid portion of the virus (freed of its protein coat) could produce tumors, indicating that, like poliomyelitis, the disease could be produced with an incomplete virus.

Although to date, no human cancer-causing virus has been found, research by grantee Dr. J. Trentin and co-workers at Baylor University in Texas touches on a long-standing suspicion that viruses which cause acute infections in man may also play a role in causing cancer. Dr. Trentin inoculated hamsters with human adenovirus 12, which may cause mild respiratory disease in man, and tumors developed in the animals. At the National Institute of Allergy and Infectious Diseases, Dr. Robert J. Huebner and colleagues, using adenoviruses 12 and 18, have obtained similar results.

Working in the opposite direction, so to speak, Dr. Hilary Koprowski and colleagues, National Cancer Institute grantees at the Wistar Institute in Philadelphia, found that Simian Virus 40 (a monkey virus shown by Dr. Bernice E. Eddy of the Division of Biologics Standards, National Institutes of Health to produce tumors in hamsters) caused bizarre changes in adult human cells growing in tissue culture. These changes were passed on to subsequent generations of cells.

Therapy of cancer has long occupied the attention of many of the Institute's grantees, and drug therapy in particular is being

intensively investigated. A technique for administering highly toxic but effective agents to the disease area with considerably reduced danger to the patient, called the isolation-perfusion technique, was introduced by Dr. Oscar Creech, Jr. and his colleagues, grantees of the National Cancer Institute at Tulane University. While the tumor-bearing area is isolated from the rest of the body by diverting the blood circulation through a heart-lung machine, drugs are introduced into the blood of the isolated area in much higher doses than could be given to the patient by ordinary means. Malignant melanomas and sarcomas have responded to this form of treatment in some instances.

The story of the significant improvements that have been achieved in the management of acute leukemia in children is described elsewhere in this report, under "Collaborative Research Programs."

Important work has been done also by Institute grantees on chronic leukemia, which is the form often found in older patients. Nitrogen mustard, related to a compound used for a war gas in World War I, was found helpful in treating this disease in the early 1940's, and since then hundreds of other alkylating agents have been developed and tried. In England, Drs. Alexander Haddow and G. M. Timmis of the Chester Beatty Research Institute working under National Cancer Institute grants, developed myleran, considered the best drug available for chronic granulocytic leukemia. Another compound, chlorambucil, has

also been demonstrated to be helpful in treating chronic lymphocytic leukemia and some types of lymphomas and other solid tumors.

Training Grants and Fellowships

The training of physicians and scientists in the fundamental disciplines in the concepts, procedures, and techniques essential to the conduct of cancer research is of major concern to the National Cancer Institute. Training of this type, directed toward preparation for academic medicine or a research career in either clinical or basic-science fields pertinent to the problems of cancer is aided by awards from the Institute. Such awards include Regular Postdoctoral or Special Fellowship Awards, Graduate Training Grants, and Undergraduate Training Grants.

The Training Branch is responsible for obtaining adequate review of fellowship and training grant applications by the Specialty Fellowships Board, the Training Grant Committee, and the National Advisory Cancer Council. The Branch administers the training grants and fellowships that are awarded, participates in the policy planning and administrative decisions that concern training grants and fellowships, initiates and modifies training programs, and conducts studies of cancer research manpower needs and requirements in space and funds necessary to initiate new programs. The results of such studies are brought to the attention of the National Advisory Cancer Council and

the Director of the Institute as bases for determining program direction.

Regular Postdoctoral and Special Fellowship Awards are made to qualified United States citizens who present satisfactory proposals for training under competent sponsors in fields or disciplines in which they can do cancer research and train others. The training may be in basic or clinical areas and may be undertaken in this country or abroad. Postdoctoral Fellowships are intended for candidates who have recently earned a Ph.D., M.D., D.D.S., D.V.M., or equivalent degree. Special Fellowships are for candidates with at least three years of relevant research experience beyond the doctorate or for applicants without the doctoral degree, who are ineligible for other fellowship support, but have a need for special training. In addition, Special Fellowships may be awarded to academicians who wish advanced specialized training.

Applications for both these awards are given preliminary review and recommendation by Panels of the Central Qualifications Board of the Division of Research Grants of the National Institutes of Health. The Panels are composed of investigators and teachers from the scientific research and teaching institutions throughout the United States. Final review and recommendation are provided by the Specialty Fellowships Board of the National Cancer Institute which is made up of

members of the Institute research and administrative staff.

Fellows of the National Cancer Institute have published research papers in the various fields of cancer research, including cancer immunology, the physiology of cell growth, growth of experimental tumors by tissue culture technique, mechanism of carcinogenesis, effects of radiation sources on cell growth, and related cancerous and normal phenomena.

This program has been in existence for 25 years; during that time many able investigators have benefited from it and contributed to the advancement of medical knowledge. In a recent survey of former Fellows of the National Cancer Institute it was found that 90.5 percent devoted some time to active research and 61.8 percent were or had been teaching.

Graduate Training Grants are made to institutions qualified to give research training in basic science or clinical areas that are particularly pertinent to the development of skilled teachers and investigators of the problems of cancer.

Training grants assist in providing the essentials for training in a wide range of medical disciplines including the following: stipends for trainees, equipment and facilities, supplies, and training personnel. This type of support allows the Program Director to

select and appoint the individuals who will receive training with the aid of the grant. The usual educational policies and practices of the grantee institution govern the use of these funds, including setting the stipend levels.

The graduate training program has assisted in providing more opportunities for attracting advanced students at all stages of development to explore new fields, learn new techniques, and broaden their areas of knowledge and interest. In many instances, training has been given to individuals who have received no direct financial assistance from the program. Many of the trainees participate in special courses in steroid biochemistry, endocrinology, genetics, histochemistry, and other fields.

Applications for this type of grant are given final review and recommendation by the National Advisory Cancer Council after preliminary review by the Cancer Training Committee of the National Cancer Institute or by another appropriate committee.

Undergraduate Training Grants are awarded for support of educational development at undergraduate levels for the purpose of 1) stimulating scientists to follow academic or research careers in scientific disciplines relevant to cancer and 2) improving the training in medical and dental schools in subjects related to cancer research,

prevention, control, and cure.

The program encourages broad training in basic disciplines essential in research on cancer. The young people educated under this program are expected ultimately to increase the number of well trained, specialized investigators in clinical pathology and pharmacology, clinical research in cancer chemotherapy, steroid physiological chemistry, genetics, analytical cytology, virology, immunology, radiotherapy, radiation biology, biophysics, biochemistry, urology, and hematology.

Special Programs

Radiotherapy Research and Training Program. In July 1961 the National Cancer Institute, with the approval of the National Advisory Cancer Council, established a major program for the broad support of a comprehensive effort in radiotherapy research and training in basic science and in clinical applications. This program has been created to meet a shortage of manpower in an area of great importance to cancer and to encourage a more scientific approach to problems in radiotherapy by providing opportunities for definitive training in experimental and clinical radiobiology and radiotherapy research and for making available the best means for such opportunities in terms of superior scientific skills and advanced radiation facilities. The program does not provide for radiation facilities for cancer therapy

unless they are essential to the major objectives of the program, which are research and training. A comprehensive program with the general objectives as defined requires for their attainment some degree of concentration of professional and scientific skills, of patients, and of major radiation research and therapy facilities and the adequate support of these research and training activities. The National Cancer Institute program is designed to help provide the support necessary to attain the objectives.

Grant aid is available to help provide support for 1) professional staff personnel (clinical, physical, chemical, radiobiological, nursing, patient care, and social workers), 2) technical workers (radiotherapy and laboratory technicians and patient care), and 3) statistical and clerical personnel.

Training stipends can be requested for 1) advanced postdoctoral clinical and laboratory training of individuals who already have the M.D., Ph.D., or equivalent degree; 2) predoctoral training leading to advanced degrees or directed toward specialized fields such as radiation physics; 3) training of medical students while engaged in special studies outside of the regular medical school curriculum; and 4) training of radiotherapy technicians.

Other needs which can be met by recommended support include costs of movable equipment and consumable supplies, travel of staff,

hospitalization, outpatient care, and fixed equipment; and with specified limitations, costs of alteration and renovation.

The purpose of the Research Career Program is to increase the number of full-time career opportunities for scientists of superior potential and capability in the sciences related to health. Grants are made to public and private nonprofit institutions in the United States in behalf of qualified candidates to enable these institutions to establish stable positions for investigators reasonably early in their careers. Two categories of awards are available: career awards and development awards.

Career awards enable institutions to finance stable positions favorable to the intellectual growth and research productivity of established investigators of high competence for the duration of their careers. Awards are made on the basis of nationwide competition among candidates whose research has won the respect of scientific leaders in their respective fields.

Development awards enable institutions to finance positions for qualified scientists who have three or more years of relevant postdoctoral research or professional experience. These awards are available for individuals with clear research potential who require additional training and experience in a productive scientific environment in preparation for careers in independent research.

The awards are also available for individuals with demonstrated capacity for independent research who have not yet reached the state in their scientific development to qualify as candidates for career awards.

These candidates are evaluated in nationwide competition with other candidates of comparable training and experience. This program relative to the fields of cancer is administered by the Office of the Associate Director for Grants and Training.

A Scientific Evaluation and Planning Grants Program has been established to permit advisory committees a measure of independence in connection with the advisory process. Grants are awarded and paid to the fiduciary of a panel to defray travel and consultatory expenses necessary for committee operation. These funds are normally intended to pay the committee members a consultant fee and to reimburse them for travel and other expenses while engaged in committee work. It is not planned that these funds be used to replace regular avenues available for the support of research projects.

The Cancer Research Facilities Program, which was renewed in fiscal years 1961 and 1962 provided funds for construction of research facilities for the conduct of cancer research in institutions unable to obtain matching funds to house existing research programs adequately. Funds in the amount of $5,000,000 were appropriated for fiscal year

1962 to make awards to institutions whose applications were recommended by the National Advisory Cancer Council in 1961 and for which funds were not then available. The authority in law under which the National Cancer Institute made these grants expired June 30, 1962.

Fiscal Review

In order to meet the needs of the expansion of the National Cancer Institute's Grants and Training Program, an Operations Branch has developed its fiscal management operations to be of maximum assistance to the applicant, grantee, program director, and staff of the National Cancer Institute and its advisory bodies. Aid is given by detailed analysis of proposed budgets submitted by applicants, review of requests for supplemental and continuing funds, and examination of expenditure reports. This operation has increased the level of financial reporting and provides related services as requested.

Collaborative Research

Chemotherapy Program

The nationwide cooperative cancer chemotherapy research program, now nearly eight years old, was set up to expedite the search for anticancer drugs through integrated research and development activities on both laboratory and clinical levels. A joint venture in which the resources of government, industry, and universities are merged, the program embraces every phase of drug research, from acquisition and screening of new materials to clinical trials and dissemination of information.

Preclinical activities, including screening and secondary evaluation of drugs, animal breeding, drug development, and various fundamental research projects, all of which are performed by non-governmental institutions under contracts from the National Cancer Institute, are administered by the Cancer Chemotherapy National Service Center. Clinical trials, conducted by cooperating physicians with grant support from the National Cancer Institute, are coordinated by the Clinical Branch.

Preclinical Activities. Cancer is now known to be not a single disease, but a group of diseases, and this has had a decisive influence on the development of the program. Solely on the basis of the types of tissues involved, human cancer can be divided into 86 different

categories, and by more rigorous criteria, into still more. The number and variety of animal tumors that could be used in screening drugs are even larger. The problem, then, is to determine which animal tumors predict the effects of drugs on specific types of human malignancy.

Until the program was launched, one mouse tumor was being used in most cancer drug screening efforts. Three mouse tumors, chosen because they would have predicted the activity of most of the drugs in clinical use at that time and because they could be utilized as a reproducible screen, were originally used in the program. Later, when it became evident that a broader screen was needed to pick up drugs of potential value in the treatment of solid tumors such as cancers of the lung, as well as leukemias and lymphomas, the primary screen was expanded to 20 tumors in mice, rats, and hamsters.

By the end of 1962, some 70,000 synthetic chemicals and 100,000 natural products, including antibiotics and a relatively small number of plant extracts, had been tested, either in the three-tumor screen or in the assay systems used for testing hormonal compounds. From this activity, many new materials that proved active to some degree in one or more types of human cancer were found, including representatives of classes of compounds not previously known to have anticancer activity.

The number of materials screened reached a peak of 50,000 one year, but has since been reduced to keep the cost of screening constant despite the increased expense of using additional antitumor screens, such as those in rats and hamsters. This year, about 6,000 synthetics and 8,000 antibiotics and plant extracts will be screened. The latter, in particular, are receiving growing attention in view of encouraging clinical results already achieved with a few plant products.

As promising new materials are found, related compounds are synthesized in efforts to find some that have greater anticancer activity and less toxicity than the parent chemical. Thus, the program utilizes both empirical and rational approaches to the search for new drugs.

To provide the large numbers of animals needed for screening, which at the inception of the program exceeded by ten times the number then available in the United States, a network of animal breeding facilities is maintained, and continuing research on animal disease control is conducted.

To assure the widest possible margin of safety in the introduction of new drugs into clinical trials, preliminary testing in small animals is supplemented by more exhaustive studies of drug effects in dogs and monkeys. Other preclinical activities include efforts to develop improved methods of drug evaluation, studies of the mechanisms of

action of drugs, and basic research leading toward the utilization of new approaches to cancer chemotherapy.

An effort is now under way to identify biochemical defects in human tumors so that drugs might be designed to correct demonstrated imbalances, and to work out methods for studying tumor specimens one at a time as a means of selecting drugs most likely to be useful in the treatment of individual patients.

A second approach currently being explored is the use of combinations of drugs which is widely believed to offer a promising way of overcoming the problem of progressive resistance of tumors to single drugs. Also in progress is preliminary work leading toward a search for chemicals that would modify the effects of radiation and for antiviral drugs.

Clinical Activities. Aside from their obvious role in identifying drugs that are clinically effective, the clinical trials represent the other side of the coin in efforts to match animal testing systems with specific types of human cancer. For it is only through comparison of large amounts of both screening and clinical data that correlations can be obtained on the basis of which results from animal tests can be used to predict drug activity in cancer patients.

Because the clinical trials phase, of necessity, did not swing into full operation until sometime after the program was launched, there is still a substantial disparity between the amount of clinical data now on hand and the huge volume of screening data. Steps were taken recently to close the gap by speeding up the clinical trials, especially those in which new drugs are tested in groups of patients representing many different types of cancer.

Only a small fraction--about one in a thousand--of all materials screened through the program has ever reached clinical trial. By the end of 1962, about 170 separate compounds had been studied. Some 27,000 patients participated in the studies.

At present, more than 700 physicians in about 150 hospitals are members of the various cooperative clinical groups. The 24 groups now in operation conduct two basic types of studies: tests of new drugs either in one or a few closely related malignancies or in a broad range of different types; and studies of drugs used at the time of surgery for a few specific types of cancer. The studies, combining surgery and drugs in particular, exemplify the kinds of investigations that the program is uniquely equipped to undertake.

The clinical phase of the program has already made numerous contributions to cancer therapy. For one thing, it has fostered major improvements in the design and conduct of drug trials, through emphasis

on the application of statistical techniques. The quality of patient care has also been substantially improved, and drug treatment has been made more widely available than it was only ten years ago.

Other Activities. Data processing and communications activities play a prominent role in the program. The system being utilized for storage and retrieval of data generated by the program is among the most advanced now in use in biomedical research. To assure prompt dissemination of information, *Cancer Chemotherapy Reports*, containing preliminary reports of investigators within and outside the program, is issued ten times a year, and *Cancer Chemotherapy Abstracts*, a compilation of abstracts of papers published in scientific journals around the world, is published monthly. In addition, screening results are published periodically as supplements to a leading cancer research journal.

Accomplishments. Two examples will serve to illustrate the ways in which the program has been responsible for advances in chemotherapy. One is the development and introduction of a new hormone for use in treatment of women with advanced breast cancer. As active as the one previously in use, the newer one causes far fewer unpleasant masculinizing effects. It was developed entirely under the auspices of the program and placed in clinical trial by the Cooperative Breast Cancer Group. The events that followed the initial clinical trials of a drug known as methyl-GAG are a second example. The drug itself was

synthesized independently, but as soon as it became clear that it was active in the type of acute leukemia that adults usually have, synthesis of a large series of closely related compounds was initiated under the auspices of the program. Investigation of these is now going on.

Acute Leukemia Task Force. The dramatic advances in the treatment of acute leukemia that provided much of the impetus for launching the chemotherapy program have been followed by additional gains in the last few years. The result has been a fourfold increase in the median survival time. Fifty percent of children who have acute leukemia now live more than a year, compared to three or four months in 1947.

There is a special sense of urgency about the search for drugs that would be effective in the treatment of acute leukemia, because it is one of those forms of cancer for which surgery and radiation are of no value. Five drugs are now considered useful in the treatment of acute leukemia in children. Each of them can induce remissions with some degree of regularity. The remissions vary in duration, and when one ends, the usefulness of the drug that induced it usually also ends. Thus, the availability of five drugs, each capable of inducing a remission in a patient resistant to one or more of the others, is an important factor in the care of acute leukemia patients.

Equally important is supportive care, for acute leukemia patients are prone to hemorrhage and infection. Hemorrhage arising from a

deficiency of blood platelets and infection in the wake of a shortage of white cells are the two most common causes of death among such patients. Thanks to a series of rapid advances in recent years, ways of coping with these crises are now becoming available. At the National Cancer Institute and a few other large cancer centers, transfusions of blood platelets are now being used to prevent and control hemorrhage. Experience with this procedure at the National Cancer Institute has shown that pooled platelets from two or more donors can be used without harmful effects, which eliminates the need for costly and time-consuming matching of the blood types of donors and recipients. In addition, inexpensive equipment has been developed that makes it possible to remove the platelets from whole blood and return the red cells to the donors, who, as a result, can give platelet donations far more often than would otherwise be possible.

Lately, the techniques used in platelet replacement have been adapted for collection and transfusion of white cells. Transfusions of this kind have cured a number of potentially severe bacterial infections in patients being treated at the National Cancer Institute.

To extend the progress already made in drug treatment and to work out the problems that need to be solved before the newer methods of supportive therapy can be widely used, the National Cancer Institute has formed an Acute Leukemia Task Force. Composed of members of the National Cancer Institute staff and representatives of a large number

of non-governmental institutions, the group meets several times a year to plan joint studies of specific problems. Its work is integrated with clinical activities of the chemotherapy research program.

At present, the chief difficulties in platelet and white cell replacement stem from the lack of methods for storing and preserving these elements. Consequently, platelet and white cell transfusions are still far from being as routine as an ordinary blood transfusion, and therefore cannot be carried out in the average hospital. An additional difficulty in white cell replacement is the low yield of white cells obtainable from the blood of normal donors. These are examples of the problems to which the Acute Leukemia Task Force is currently addressing its efforts.

Virology Research Resources Branch

As virus-cancer research began to expand during the second half of the 1950-1960 decade, it became apparent that greatly increased quantities of certain resources would be needed if modern virological techniques were to be applied to the cancer problem. The Virology Research Resources Branch administers a program oriented toward developing these resources and making them available to virus-cancer investigators.

The program is implemented by contracts, with one exception, and close working relationships are maintained between staff members

and contractors, on the one hand, and National Cancer Institute grantees working in the virus-cancer field, on the other.

A good start has been made toward meeting investigators' needs for cell cultures whose origin and essential characteristics are known, thus permitting their use in efforts to propagate viruses that may be present in human cancer tissue. By the end of 1962, fourteen human and animal cell strains had been characterized (the only segment of the program implemented by grants) and a cell bank put into operation.

One contractor has begun producing significant numbers of germ-free mice on a weekly basis. Typing reagents for a number of mouse viruses have been developed and produced in quantity. The responsibility for a program on human viral reagents, which was initiated under this program, has been transferred to the National Institute of Allergy and Infectious Diseases.

In recent months, staff members of the Virology Research Resources Branch have taken over responsibility for implementing administrative and program decisions pertaining to virus-cancer research that are made by the National Cancer Institute's Scientific Directorate and the Human Cancer Virus Task Force. They are also functioning as a center for collection and dissemination of virus-cancer research technical information.

Diagnostic Research Branch

The urgency of early detection and diagnosis of cancer can hardly be overemphasized. The success of the cytologic test for uterine cancer is a case in point. Thanks largely to its increasingly widespread use in this country, there has been an almost 50 percent drop in uterine cancer mortality since 1940.

The responsibility for developing techniques of comparable efficiency for detection and diagnosis of other forms of cancer is now assigned to the Diagnostic Research Branch of the National Cancer Institute. Established late in 1960, after the Congress had earmarked funds for a substantially enlarged diagnostic research effort, it operates a program of contract-supported investigations integrated with research in its own laboratories.

The program is built around three basic assumptions. One is that the likelihood of developing one diagnostic test for all forms of cancer is as remote as the chances of finding a universal cure. Second, it is assumed that there is a good chance of developing biochemical or immunological means of diagnosing certain forms of cancer at an early stage, especially those forms in which an abnormality accompanying the cancer is manifested by an overabundance of a chemical or biological product. The third assumption is that most, if not all, cancers share certain secondary phenomena that warrant investigation.

Necessarily a long-range effort, in light of the major gaps in present knowledge, the program is oriented not only toward developing and testing new techniques, but also toward providing for research investigators the biological materials, including human tissue and serum, needed for such work.

The diagnostic approaches being explored fall into four categories: chemistry, pathology, cytology, and immunology. At present, diagnosis of cancer rests on thorough physical examination and study of case history, radiologic examination, and pathology, including biopsy and cytology, or the study of cells sloughed off by the tumor. The role of clinical chemistry, which includes studies of enzyme and hormone levels in blood and other body fluids, has been strong but essentially secondary. The potential value of histo-chemistry--the study of chemical substances in tissues--and immunology has received little attention until now. Cytology, the basis of the uterine cancer test, is being investigated for its possible application to detection of cancer of other sites.

Field Studies

Organization

Research activities dealing with carcinogenesis, epidemiology, and biometry are centralized under the Associate Director for Field Studies. Leadership is thus provided for the coordination of activities in these areas both as direct research activities and in cooperation with investigators in universities, medical centers, and health agencies located throughout the United States and abroad.

Biostatistical Research

The Biometry Branch employs the methods of mathematical and analytical statistics in independent and cooperative studies. These may be applied to laboratory research on carcinogenesis and chemotherapy, investigation of the distribution of cancer among populations, and evaluation of therapeutic measures in clinical trials. Staff members consult and collaborate with investigators in other areas of the Institute or those of other institutions in the United States and abroad, on the initiation and design of experiments and the analysis of results.

Current investigations of the Biometry Branch include collaborative studies with scientists in several parts of the world. The object here is to observe the statistical changes in cancer morbidity for individuals or groups who move from one environment to another in a change of residence. For example, one recent finding was that smokers who move frequently from one community to another are more likely to develop lung cancer than less mobile persons and that the risk is

greatest for heavy smokers moving from rural to metropolitan areas and for the foreign-born settling in large U.S. cities. A comparative study is being made of the relationship of customs and personal practices to the incidence of cancer of the lung and stomach among the Japanese in Japan, Hawaii, and California. A similar collaborative study to learn what factors influence the cancer risk for people who migrate from Poland to the United States is being developed with the Polish Ministry of Health and the National Cancer Institute of Poland.

Studies in the Causation of Cancer

The Carcinogenesis Studies Branch conducts independent and cooperative investigations of factors in human environments that may have a causal relation to cancer. This Branch is also undertaking to develop improved methods for testing carcinogenic chemicals and to determine whether a minimum cancer-causing dosage level exists for such agents both in animals and in man. The work is being conducted through intramural investigations, the use of contracts to extend intramural research, and through collaborative studies with other agencies, including government agencies.

An interagency project was recently arranged in which the Institute will collaborate with the Atomic Energy Commission on studies of the interaction of radiation and chemicals as a possible cause of cancer in animals, with emphasis on fundamental investigation of the carcinogenic process. This work, which may be expanded later to include the investigation of the role of viruses in this process, is being done at

the Oak Ridge National Laboratory which is operated for the Atomic Energy Commission by the Union Carbide Corporation.

Laboratory studies on the test animals suggest that viruses may interact with chemicals to cause cancer. In one experiment, mice exposed to influenza virus plus air polluted with ozonized gasoline fractions developed lung tumors similar to the most common type of lung cancer in man. Neither the virus nor the chemically polluted air alone caused such tumors; they appeared only when the two were combined.

The causal relationship of environmental factors to the onset of human cancer is also the concern of studies carried out through the Environmental Cancer Section. Experimental studies of samples of polluted water and air as related to the causation of cancer in laboratory animals are in progress.

Epidemiological Surveys

The Epidemiology Branch does independent and cooperative studies of the nature and extent of cancer in human and animal populations. Surveys are developed to determine morbidity trends in selected human populations and the relationship of morbidity to racial, genetic, ethnic, environmental, occupations, geographic and socioeconomic factors.

During the past year epidemiologic studies of cancer in childhood have been emphasized since laboratory studies in animals have shown that, in general, the embryo and newborn are more susceptible to environmental carcinogens than are more mature members of a species.

It is believed, too, that the relationship between cancer and its cause may be more readily determined from studies in childhood cancer because pediatric histories are notably less cluttered with extraneous circumstances than are the histories of adults.

Through the development of field stations at children's hospitals with large volumes of cancer cases, an attempt is being made to use as fully as possible information already collected on hospital charts. During 1962 such a field station was established at the Los Angeles Children's Hospital. Previously established field stations are located at Boston Children's Hospital and Pittsburgh University Hospital.

The epizoology section, placed temporarily at Michigan State University, has developed a strong program of research on domestic animal populations, especially cattle, and is planning a series of animal tumor registers. Preliminary studies have indicated that the distribution of certain types of cancer in animals may have very important implications in the genesis of cancer in man.

Research Progress

Epidemiological studies were responsible for confirmation of the laboratory observation that cancer of the uterine cervix can exist in a stage called carcinoma-in-situ for several years before becoming frank, invasive cancer.

To test the possibility that the cytologic examination worked out by Papanicolaou and Traut, known as the "Pap" smear, might be employed

as an aid to diagnosis of cancer of the uterine cervix, the National Cancer Institute in 1947 established a pilot study at Hot Springs, Arkansas. On the basis of this experience, the Institute in 1952 moved the project to Memphis, Tennessee for full-scale study of the feasibility of the cytologic test as a case-finding technique among large populations.

With the cooperation of the University of Tennessee Medical School and local health and medical authorities, a project was established for the purpose of applying the test to 165,000 women in the City of Memphis and Shelby County.

Among the first 108,000 women given the test, some 800 cases of cancer were detected and subsequently diagnosed microscopically. About half of these proved to be carcinoma-in-situ which has a cure rate approaching 100 percent. Fully 90 percent of these cases were totally unsuspected. The other 400 cases were invasive cancers in different stages, 30 percent of which were also unsuspected.

A year later 33,000 of these same women were retested and 83 cases of cancer were detected, of which 72 were preinvasive and 11 invasive. The invasive cancer rate on the second screening dropped from 3.4 to 0.3 per thousand.

In addition to the Memphis project the National Cancer Institute supported a number of other studies to expand the use of the cytologic test. This procedure is now accepted in many areas of the country and

its widespread use is credited partially for a steady decline in the death rate for uterine cancer. In 1940, the age-adjusted death rate per 100,000 females was 25.5 for this type of cancer. By 1959, this figure had dropped to 14.0.

Great progress has been made in the techniques of collecting vital statistics on cancer. The National Cancer Institute carried out the first large-scale survey in ten metropolitan areas of cancer incidence in the United States in 1937 and repeated the operation in 1947 to produce comparative data on variations in the incidence of cancer by age, sex, race, geographic region, marital status, and type and primary site of disease.

The development of modern statistical techniques has also been vital to the sound evaluation of end results with different cancer treatments and for greatly improving the foundations for screening agents for anti-tumor or cancer-causing effects.

National Cancer Institute scientists were among the first to show that cancer-causing agents are present in the atmosphere. In 1942 one group of Institute investigators reported that tars extracted from the atmospheric dusts of several American cities produced malignant tumors in mice. Identification of cancer hazards arising from industrial processes makes possible corrective measures. For example, workers in the chromate and chromium-compound-producing industries are now being protected as a result of investigations carried out cooperatively by an Institute scientist and others.

Research Progress

Cancer research has been advanced immeasurably during the life of the National Cancer Institute. The examples of accomplishments in the laboratory and clinic cited in this report are but a few of the important gains made possible by the Institute's conduct and support of research and training. The scientific literature abounds with original contributions to research progress in this field by investigators of many disciplines, and the results of their efforts have given physicians, health administrators and the public new weapons and new hope against cancer.

NATIONAL HEART INSTITUTE

The National Heart Institute was established in the Public Health Service by Section 411 of the Public Health Service Act as amended by Public Law 655, the National Heart Act. The measure, introduced in both houses by bipartisan groups, was unanimously passed by Congress in the summer of 1948 -- the second session of the 80th Congress. It was signed into law by President Truman on June 16, 1948.

The National Heart Act provides for "a National Heart Institute", a "National Advisory Heart Council" to counsel, and conduct and support heart research and training and aid to the states with the purpose "to improve the health of the people of the United States."

On August 1, 1948, the National Heart Institute was designated as one of the Institutes in the National Institutes of Health, with headquarters in Bethesda, Maryland. On that same hot summer day, the NHI began to take shape as two typewriters, chairs, and a couple of file cabinets were moved into two rooms in a two-story temporary building that progress recently replaced with a parking lot next to an impressive new structure.

Doctor C. J. Van Slyke, physician-researcher and medical administrator who started the PHS research grants program in 1946, was named first director of NHI.

The new Public Health Service heart program was off to a fast start. The National Advisory Heart Council, a distinguished body of eminent heart disease authorities and leaders in other fields, was soon set up as authorized by the National Heart Act to advise and make recommendations on policy and development of the program. By the end of the year, with objectives well in focus, long-range programs had been undertaken and were running smoothly. An impressive beginning had been made.

From those first days until the present, the National Heart Institute, through dedicated scientists and funds appropriated annually by Congress, has taken the lead in the fight against the nation's number one killer -- heart disease.

From its modest beginnings with only a handful of employees in 1948, the NHI has increased its staff to 624 as of 1963. The first NHI budget, appropriated by Congress in 1949 was $2,897,114. By the end of 1963, it is estimated that NHI will spend $107 million. The President's budget for 1964 is $133,624,000.

MAGNITUDE OF THE PROBLEM

Many people speak of heart disease as one disease with one still unknown cause. "Heart disease" is really a general term used to describe nearly 20 diseases affecting the heart and circulatory system. Physicians call them the cardiovascular diseases.

Most have well-known names -- atherosclerosis, high blood pressure, rheumatic fever, and congenital heart defects. Others, such as bacterial endocarditis, pulmonary arterial hypertension, and cardiovascular syphilis, are not so well known.

In combination, the cardiovascular diseases claimed an estimated 947,210 lives in 1962 -- more than half of all the deaths which occurred in the U. S. during the year. One-third of these heart victims had not yet reached the retirement age of 65. In addition, 10 million Americans living today have some form of cardiovascular disease.

Each year, in industry alone, more than 25,000,000 workdays are estimated lost because of cardiovascular diseases. This figure does not even include those persons who cannot work at all because of a heart disease. The cost in lost productivity of people in the total labor force disabled by heart disease, while incalculable precisely, is estimated to run toward billions of dollars.

Complete death-rate breakdowns for 1962 are, of course, not yet available. However, 1961 figures show that arteriosclerotic heart

disease, which includes coronary disease or "heart attacks," accounted for 502,351 deaths -- more than half of the total heart figure. Strokes accounted for 192,951 deaths and high blood pressure claimed 75,467.

The elderly have no claim to a monopoly on heart deaths. Heart disease was listed as the cause of death on 25 percent of all who died between the ages of 25 and 44. In the 45 to 64 age bracket, 50 percent of all deaths were caused by heart disease.

In the last 10 years, heart deaths increased from 776,114 in 1952, to 924,622 in 1961. This rise can be attributed to the general aging of the population and the upswing of the arteriosclerotic heart disease death rate. In 1952, this death rate was 226 per 100,000 population. In 1961, it was 275 per 100,000, an increase of 22 percent.

The death rate for strokes and other vascular lesions in the brain, remained about the same.

Three heart disease categories have shown dramatic decreases over the same period. Rheumatic fever and chronic rheumatic heart disease -- down 28 percent; non-rheumatic chronic endocarditis and other myocardial degeneration -- down 38 percent; and high blood pressure -- down 33 percent.

NHI ORGANIZATION

Programs of the National Heart Institute are planned in response to recognized and essential needs and thus they constitute working means toward eventual attainment of its main objective, the conquest of cardiovascular diseases.

The Institute has specific responsibility for 1) conducting, fostering, and coordinating research and training on the causes, prevention, diagnosis, and treatment of diseases of the heart and circulation and for conducting research on the nature of the aging process; 2) providing grants-in-aid to public and private institutions and individuals for cardiovascular research and teaching; 3) providing training and instruction in both research and clinical aspects of the heart diseases; and 4) collecting and disseminating information on cardiovascular diseases and the aging process. These responsibilities are carried out through the offices of the Director, the Director of Intramural Research, the Associate Director for Collaborative Studies, and the Associate Director for Extramural Programs, and groupings of branches and laboratories comprising the designated areas.

The Intramural Research program conducted by the Heart Institute is directed toward increasing fundamental and clinical knowledge of the underlying disease processes affecting the heart and circulatory system and toward developing information that will enable the prevention or amelioration of these diseases. The Institute's research approach is multi-disciplined, involving chemical, biochemical, physiological, pharmacological, bioengineering, medical and surgical skills.

The Intramural Research organization is comprised of seven laboratories --Biochemistry, Cardiovascular Physiology, Chemical Pharmacology, Clinical Biochemistry, Kidney and Electrolyte Metabolism, Metabolism, and Technical Development -- and five branches -- Cardiology, Clinical Endocrinology, Experimental Therapeutics, Gerontology, and Surgery. Each of these research groups is made up of a number of smaller units working with separate facilities on a variety of related studies.

The Collaborative Studies activities of the National Heart Institute have the following general aims: to carry out epidemiological, geographical pathology, biometrics, dietary, and related studies of cardiovascular disease directly or in collaboration with interested researchers; provide consultation and assistance to researchers and organizations requesting help in such studies; train personnel for work in this field; and maintain liaison with other groups having interest in this field, nationally or internationally.

Organizational units of the Collaborative Studies include the Framingham Epidemiology Section, which is conducting a long-term community study of constitutional and environmental factors related to heart disease; the Field Epidemiological Research Section, which carries out a variety of studies aimed at identifying factors and conditions that cause disease; the Geographic Pathology Section, which is studying differences in severity or frequency of heart disease in selected population groups; and the Biometrics Research Branch, which conducts research in biometrics methods and theory, and provides statistical assistance and consultation to Institute scientists.

The Extramural Programs of the National Heart Institute provide extensive support for cardiovascular research and training. Through the research grants

program, heart disease research is stimulated and supported in communities, hospitals, and other research institutions throughout the nation. The grants have made possible the expansion of heart research activities, the initiation of new studies, and the fostering of projects in neglected areas of investigation. The fellowships program is serving to increase the number of trained heart disease investigators and to help assure a continuing flow of skilled and imaginative workers into the cardiovascular field. The training program of the Institute, with grant support provided to medical and some other schools at undergraduate and graduate levels, is helping improve cardiovascular education and the quality of research training, attracting promising students to medical research careers and increasing the number of cardiovascular scientists, teachers, and highly trained physicians.

The organization for Extramural Programs administration consists of five branches. The Research Grants Branch administers the regular research grants program for cardiovascular research, the Program Projects Branch administers the Heart Institute extramural research program project and clinical research center grant programs, the Special Research Projects Branch administers the special research grant programs for cardiovascular research, such as cooperative research projects and support for conferences and publications; the Training Grants and Awards Branch administers the Heart Institute extramural training programs; and the Operations Branch provides over-all management functions to the extramural program areas.

The Heart Information Center, organizationally a part of the Office of the Director, carries out the responsibility for collecting and

disseminating information. A steadily developing program of public and professional information is conducted, utilizing all media.

NHI STAFF

The National Heart Institute had 622 full-time personnel and 83 part-time or intermittent employees as of December 31, 1962. Of the full-time employees, 137 were in the Public Health Service Commissioned Corps, 28 were Visiting Scientists, 2 were Staff Fellows, and 455 were in Civil Service. Classified by occupational grouping, 351 were professional and scientific personnel, 104 were sub-professional and technical support personnel, 166 were in administrative, clerical and office services, and 1 was in the plant operation and maintenance category.

Excluding the visiting scientists, 190 of the Heart Institute employees held doctoral degrees. One hundred fifty-five of these doctors were in the Intramural Research program and 45 were in other Heart Institute activities.

BUDGET SUMMARY

Amounts available for obligation:

	1963
Appropriation	$147,398,000
Comparative transfers to other accounts	-18,124,000
Unobligated balance brought forward	+1,000,000
Unobligated balance carried forward	-435,000
Transfer to "Operating expenses, PBS," GSA	-46,000
Total	129,793,000

Obligations by activities:

Grants:

Research	$82,661,000
(Indirect costs at 20%)	(1,065,000)
(Additional indirect costs)	0
(General research support grants)	(5,900,000)
(Categorical clinical research centers)	(3,000,000)
(Scientific evaluation and planning)	(25,000)
Fellowships	5,950,000
(Research career awards)	(2,150,000)
Training	14,000,000

Direct operations:

Research	10,483,000
Collaborative studies	1,323,000
Training activities	200,000
Review and approval of grants	1,904,000
Program direction	530,000
Gerontology Building	$565,000
Total obligations	117,616,000
Unobligated balance reserve	12,177,000
Total obligations and reserve	129,793,000

INTRAMURAL RESEARCH

The intramural research program of the National Heart Institute is directed primarily toward the acquisition of basic knowledge about the structure of the body and its biochemical and physiological functions. The emphasis is placed on basic research because the cardiovascular diseases appear to have their roots in the subtle and complex processes of metabolism and in the mechanisms that regulate those processes. Thus, such basic studies offer the most promising approach for getting at the underlying causes of these diseases, and, on the basis of such knowledge, seeking means of prevention and cure.

At the same time, thanks to the excellent patient-care facilities provided by the NIH Clinical Center, the Heart Institute also conducts a vigorous research program aimed more directly at the solution of specific clinical problems posed by cardiovascular disease. Further, the close association between the basic and clinical research laboratories makes possible the more rapid clinical testing and application of those basic findings which show promise in the solution of clinical problems.

THE LABORATORY OF BIOCHEMISTRY.....conducts research on the synthesis, structure, and function of proteins. Major areas of study include: (1) Genetic factors determining the structure of enzymes, the protein "executives" that expedite the biochemical transactions of the body. (2) The structure of the contractile proteins myosin and actin, the nature of their interaction during the contraction of muscle, and the mechanism whereby the chemical energy of adenosine triphosphate (ATP) is harnessed to drive the contraction process.

(3) The function of enzymes in the reactions of intermediary metabolism, wherein fragments originating from the breakdown of more complex substances are converted to energy, or else used as building blocks in the assembly of other complex substances needed by the body.

THE LABORATORY OF METABOLISM.....conducts research on the complex processes by which fats and fat-like substances are synthesized, transported, and broken down by the body. Of particular interest are nerve and hormonal mechanisms that regulate these processes. If, as many believe, atherosclerosis is primarily a disorder of metabolism, a fuller understanding of these processes might result in means of preventing the disease, retarding its development, or perhaps even reversing its course.

THE LABORATORY OF TECHNICAL DEVELOPMENT.....applies the techniques of engineering, electronics, and biophysics to the development of instruments and methods for solving biochemical and physiological problems encountered in cardiovascular research.

THE LABORATORY OF CHEMICAL PHARMACOLOGY.....investigates: (1) the actions of drugs on the body, especially their interaction with nerve, hormonal, and metabolic processes; and (2) the action of the body on the drugs.

Such studies may provide specific clues to the relationship between drug structure and function, and hence to drugs specifically designed for the job they are to perform. Moreover, knowledge about the changes in

drug structure brought about by its metabolism may provide important information about the mechanisms that cause those changes. It has also resulted in the development of new drugs on more than one occasion.

THE EXPERIMENTAL THERAPEUTICS BRANCH.....is concerned with the development, evaluation, and application of new or improved methods of treatment in patients suffering from cardiovascular disease. Their major research efforts are directed toward the study of hypertension and the evaluation of new drugs for treating it. In addition to assessing the clinical effectiveness of these drugs, these scientists also study the mechanisms by which such drugs affect blood pressure. Such knowledge might provide valuable leads to the development of more effective drugs for treating hypertension and may also provide clues to the underlying causes of the disease itself.

THE LABORATORY OF CLINICAL BIOCHEMISTRY.....conducts research dealing with the biochemical mechanisms of metabolism and with disease-induced alterations in these mechanisms. A major area of study is the metabolism of amines. Since many drugs currently used against hypertension affect amine storage, synthesis, or destruction, scientists of LCB frequently employ these drugs as research probes in the study of amine metabolism. They also cooperate closely with the NHI Experimental Therapeutics Branch in laboratory and clinical studies evaluating such drugs.

THE LABORATORY OF KIDNEY AND ELECTROLYTE METABOLISM...is concerned with research on the physiology of the kidney and on the mechanisms by which

it maintains fluid balance, acid-base balance, and electrolyte balance in the body. Other important studies are centered on the roles played by hormones from the pituitary, adrenal, and other endocrine glands as regulators and modulators of these processes. The little-understood mechanisms of active transport, whereby the cells of the body expend energy to move substances across their membranes against opposing concentration or electrical gradients, is another major area of study.

THE CLINICAL ENDOCRINOLOGY BRANCH.....conducts laboratory and clinical studies on the basic physiology of the adrenal cortex and parathyroid glands, on the roles played by their hormones in metabolism, and on disease-induced alterations in their function. Particular emphasis is given to research on the synthesis, release, and metabolism of aldosterone and other adrenal cortical hormones.

THE LABORATORY OF CARDIOVASCULAR PHYSIOLOGY.....is currently investigating the numerous regulatory mechanisms that adjust heart performance to conform with the circulatory requirements of the body's organs and tissues. Special attention has been given to the nerve and hormonal pathways which can affect heart work and output by their influence on the activity of the atria.

THE CARDIOLOGY BRANCH.....conducts research on the basic physiology of the cardiovascular and pulmonary systems and on the development of improved methods for assessing the functional capacity of these systems in health and disease. Special emphasis is given to the development of improved techniques of cardiovascular diagnosis particularly for the precise diagnosis and localization of congenital and acquired heart defects.

THE SURGERY BRANCH.....is concerned primarily with the development of new methods for the surgical treatment of patients with congenital or acquired heart disease. New techniques are tested against heart lesions produced experimentally in laboratory animals. Those techniques whose merit is proved by rigorous testing in animals may subsequently be applied clinically.

THE GERONTOLOGY BRANCH.....conducts research directed toward (1) describing the biochemical, physiological, and psychological changes that occur with increasing age in man; and (2) investigating the basic mechanisms that bring about those changes. These studies explore the effects of aging on the whole organism, on individual organs and tissues, and on individual cells and components. The subjects studied range from man down to the simplest protozoa.

INTRAMURAL RESEARCH PROGRESS

ATHEROSCLEROSIS

Cholesterol. There is a formidable body of statistical evidence that elevated serum cholesterol levels greatly increase the risk of developing atherosclerosis. Frequently, elevated serum cholesterol levels can be traced directly to the diet, and corrected by reducing its total fat calories and substituting vegetable or marine oils, high in unsaturated fats, for animal fats high in cholesterol and saturated fats.

Such dietary measures are very often successful in controlling serum cholesterol levels, and they need not produce any major upheaval in habitual dietary patterns. However, many cases of hypercholesterolemia do not respond

to such diets, largely because the liver can manufacture cholesterol from any item in the diet from soup to nuts. Thus the search continues for drugs that can reduce serum cholesterol levels by inhibiting the synthesis of cholesterol by the liver.

But much more must be learned about the metabolism of cholesterol and the compounds used in its production before the blockade of cholesterol synthesis can be attempted with any assurance that this blockade will do more good than harm.

NHI studies conducted this year have been concerned with the steps involved in cholesterol synthesis once the basic sterol nucleus has been laid down. In these studies, Triparanol (Merrell), a drug that blocks cholesterol synthesis, has proved to be a valuable research tool.

When cholesterol synthesis is blocked with this drug, the fall in blood tissue concentrations of cholesterol is accompanied by increased concentrations of desmosterol, a compound identical to cholesterol except for two missing hydrogen atoms in the sterol side chain. Thus it appeared that desmosterol was the immediate precursor of cholesterol.

Subsequent studies have shown that desmosterol is only one of many possible sterol precursors of cholesterol, and, in the general scheme of cholesterol synthesis, may be of minor importance. It appears that the enzyme responsible for adding two hydrogen atoms to desmosterol is not highly specific in its action. It performs the same function for a number of other sterols which can be used in the synthesis of cholesterol. Although desmosterol is

the major sterol accumulating in tissues when this enzyme activity is inhibited, there are also increases in the tissue concentrations of a number of other sterols with unsaturated side chains and decreases in the concentrations of sterols with saturated side chains.

Fatty Acids. Adipose tissue provides a major reserve depot for metabolic fuels needed to sustain the organism during periods of fasting, increased physical activity, or stress. Under such circumstances, the triglycerides (neutral fat) stored in this tissue can be broken down and their free fatty acids (FFA) released into the circulation to meet current energy demands.

NHI studies indicate that two keys are needed to unlock these energy reserves. One is provided by the adrenal cortex, the other by the sympathetic nervous system. If either key is lost, the animal can draw only on those metabolic fuels already present in his blood. As this supply dwindles, it cannot be replenished from his fuel reserves. When it is gone, so is he.

Thus, if an animal is deprived of his adrenal cortex and is subsequently exposed to cold or forced to perform muscular exercise, his body temperature falls rapidly and he dies within a few hours. These dire consequences are prevented if he is treated with any of several adrenocortical hormones; but norepinephrine or epinephrine, normally potent FFA mobilizing agents, have no such protective effect.

If the animal's adrenal cortex is left intact, but his sympathetic nervous system is knocked out with drugs, he also succumbs rapidly when

subjected to cold or exercise. This can be prevented by treating him with norepinephrine or epinephrine, but not by treatment with adrenocortical hormones.

In the mobilization of FFA, norepinephrine, the chemical messenger of the sympathetic nervous system, is released directly into adipose tissue by sympathetic nerve discharges. Norepinephrine stimulates FFA release by stepping up the activity of lipases: enzymes which break down triglycerides. However, norepinephrine appears to be unable to activate these enzymes unless adrenocortical hormones are also present.

Lipoproteins. Lipoproteins are large fat-protein molecular complexes that carry about 95% of the lipids found in serum. They are divided into two weight classes: high-density and low-density lipoproteins. Although the distribution of serum lipids between these lipoprotein classes appears to be a factor determining relative susceptibility to atherosclerosis, the precise roles played by the two classes in human fat metabolism have remained obscure.

Currently under study by NHI scientists is a disorder of lipid storage that may help to clarify these roles. Tangier disease is characterized by the accumulation of large quantities of cholesterol in tonsils, liver, spleen, and other reticuloendothelial tissues, and by a virtual absence of serum high-density lipoproteins. Thus, the four cases of Tangier disease discovered so far provide unique opportunities to study the role of lipoproteins in the metabolism of lipids, especially cholesterol. The clinical manifestations of the disorder indicate that the high-density fraction may play some essential

role in the handling of cholesterol by the body, and current studies are seeking to discover just what that role might be.

Tangier disease also appears to be genetically determined, and thus provides opportunities to study genetic factors operating in the synthesis of high-density lipoproteins.

HYPERTENSION

Many recent advances in the drug treatment of hypertension have stemmed primarily from increased scientific knowledge about the metabolism of amines. These are nitrogen-containing compounds made by the body from the amino acids of dietary protein. Several are powerful stimulants that increase heart rate, heart output, and blood pressure. Two of them--the catechol amines norepinephrine and epinephrine--have long been suspected of playing some nefarious role in hypertension, but neither they nor any of their chemical relatives have ever been convicted.

Nevertheless, many drugs currently used against hypertension appear to owe their effects on blood pressure to their effects on amine metabolism. The amine figuring most prominently in the action of these drugs is norepinephrine. Norepinephrine, a chemical transmitter stored at most sympathetic nerve terminals, is liberated by sympathetic nerve impulses to convey their messages to target organs. Among these targets are the muscles in the walls of blood vessels. Drugs which interrupt this chemical messenger service can prevent blood-vessel constriction by halting vasoconstrictive messages short of their targets.

One such drug, alpha-methyl DOPA (Aldomet, Merck Sharp & Dohme), strikes at the mechanisms which maintain norepinephrine stores at sympathetic terminals.

The norepinephrine normally held in reserve there is turned loose to be set upon and destroyed by enzymes. Eventually too little is left to handle sympathetic nerve traffic.

Alpha-methyl DOPA has continued to perform impressively against hypertension, including the malignant phase of the disease, in long-term clinical studies at NHI. It is a powerful hypotensive agent, especially when used in conjunction with thiazide diuretics. Its smoothness of action, relative freedom from adverse side effects, and mild tranquilizing properties make alpha-methyl DOPA the drug of choice for many hypertensive patients. The drug has recently been placed on the market for use by physicians.

Another blood-pressure drug that has recently been placed on the market following successful clinical trials at NHI is MO-911 or pargyline (Abbott). This drug belongs to a family of compounds called monoamine oxidase inhibitors. These block the action of an enzyme largely responsible for inactivating norepinephrine, epinephrine, and a number of other amines. Several MAO inhibitors are powerful hypotensive agents. Although nobody could explain why slowing the destruction of such powerful stimulants as norepinephrine should lower blood pressure, there appeared to be a direct relationship between the potency of these drugs as MAO inhibitors and their potency as hypotensive agents.

Recent NHI studies may have provided the answer to this riddle. Their findings indicate that certain MAO inhibitors may block sympathetic transmission by preventing the release of norepinephrine at sympathetic terminals.

This heretofore unsuspected action of MAO inhibitors provides a plausible explanation for the blood-pressure effects of certain of these drugs.

CONGESTIVE HEART FAILURE

When the heart is taxed with excessive circulatory burdens by hypertension or other factors, a number of mechanisms help the heart to meet its circulatory obligations by increasing its pumping efficiency. If the demands imposed upon the heart become exorbitant, even these compensatory mechanisms may not be enough, and the heart goes into failure.

One of the most important of these compensatory mechanisms is provided by the sympathetic nervous system. Sympathetic nerve discharges release norepinephrine in the heart. This amine augments heart output by increasing heart rate and also the vigor of heart muscle contraction. NHI studies indicate that the heart may keep its sympathetic nerve terminals fully "charged" with norepinephrine by either of two mechanisms. The heart readily takes up and stores norepinephrine from the circulation; it also has all of the enzymatic machinery needed to synthesize norepinephrine from the amino acid tyrosine.

The important role of the sympathetic nervous system in providing support to the failing heart was demonstrated in two clinical studies by NHI scientists. In the first, the scientists compared sympathetic activity during exercise in normal subjects with that in patients with congestive heart failure. In every instance, sympathetic activity was significantly higher in the patients.

In the second study, they administered guanethidine, a blood-pressure-lowering drug that inhibits sympathetic activity, to 10 patients with "borderline" congestive heart failure. The drug clearly increased the symptoms of

heart failure in 5 of the 10. Because many patients with congestive failure are also hypertensive, this finding underscores the need for extreme caution when using drugs in patients with limited cardiac reserve.

When the body's own compensatory mechanisms prove inadequate to keep the heart from lapsing into failure, digitalis and related cardiac stimulants are commonly used to augment heart output. Because these drugs do not increase heart output in normal subjects, scientists have questioned whether they have any effect on the normal heart.

NHI studies have shown that these drugs do increase the vigor of contraction in normal as well as in failing hearts. In normal subjects, heart output does not increase because the drugs also cause peripheral blood vessels to constrict. As a result, the gain in heart contractility is largely offset by the increased resistance against which the heart must work. In patients with congestive heart failure, however, these drugs increase heart contractility while decreasing peripheral resistance. The reason for these strikingly different effects is not clear.

Another compound that has been reported to be a cardiac stimulant possibly useful in the treatment of congestive heart failure is angiotensin. Angiotensin, a powerful blood-vessel constrictor, is produced in the body through the interaction of renin (a hormone from the kidney) with a plasma protein. The effects of angiotensin on blood-pressure have been intensively studied, but considerably less is known concerning its effects on the heart itself.

NHI studies, assessing the action of angiotensin on the heart, raise some doubts concerning the use of angiotensin in cases of congestive heart

failure. The drug has little direct effect upon the heart, and that is to decrease its contractility somewhat. The drug caused an immediate sharp rise in blood pressure, thus increasing the resistance against which the heart was working. However, heart rate and contractility did not increase until later. These later effects appeared to result from sympathetic stimuli, possibly arising from peripheral receptors.

Aldosterone. A hormone from the adrenal cortex, aldosterone promotes salt retention by the kidneys, sweat glands, and certain other tissues. Salt depletion or factors reducing blood pressure or blood volume usually lead to increased aldosterone production and secretion. However, the immediate stimulus is provided by still another hormone.

Earlier studies had shown that the hormone which stimulates aldosterone secretion was produced by the kidney, but neither identified the hormone nor defined the nature of the mechanisms that triggered its release.

Subsequent studies have shown that the substance derived from the kidney is renin. The stimulus for its release appears to be a fall in renal artery pressure or flow. In the plasma, renin catalyzes the formation of angiotensin, which triggers the release of aldosterone from the adrenal cortex.

CONGENITAL AND ACQUIRED HEART DEFECTS

Diagnosis. One of the most important contributions made by NHI scientists to cardiovascular diagnosis has been the transseptal technique of catheterizing the relatively inaccessible left heart chambers.

The technique involves passing a catheter into the right atrium. A hollow needle is then passed up this catheter and used to puncture the muscular partition (septum) separating the right and left atria. A second catheter is then passed through the needle into the left side of the heart.

Since its development, the transseptal technique has proved its worth in more than 450 cases. Recent modifications have further increased its safety and usefulness in diagnosis, and it is now clearly the technique of choice for left-heart catheterization.

Idiopathic subaortic stenosis is a rare heart disorder only recently recognized as a clinical entity. The muscles of the left ventricle are greatly enlarged, particularly in the outflow region just below the aortic valve. This oversized band of muscle contracts as the ventricle contracts, constricting the outflow tract and interfering with the ejection of blood.

Scientists of the Cardiology and Surgery Branches have devised techniques for diagnosing this disorder and criteria for selecting patients for palliative surgery. Diagnosis had been difficult because the degree of obstruction produced by the defect is directly dependent upon the vigor

of ventricular contraction. Thus it can vary widely from time to time in any given patient, and even from one cardiac cycle to the next.

Severe obstruction, which can lead eventually to congestive heart failure and death, can be relieved in many cases by cutting through the obstructing band of muscle. Since digitalis and similar heart stimulants only increase the degree of obstruction, they should never be used to treat heart failure in such cases.

Surgery. An important segment of NHI research in cardiovascular surgery deals with the design, construction, and evaluation of artificial heart valves. Of great importance in determining the ultimate success or failure of such a valve are the materials used in its construction. These materials must neither affect nor be affected by body fluids or tissue; must retain their strength and elasticity over years of constant hard use; must not promote the formation of clots; and must be porous enough to allow the ingrowth of host tissue, which is essential to firm healing.

In some cases this tissue ingrowth can also pose problems. If the material used in the construction of valve leaflets is too porous, excessive ingrowth of fibrous tissues may make the leaflet too stiff to open and close properly. In investigations to determine how large the pores of such material should be for optimum performance, NHI scientists are working with a material composed of alternating fibers of dacron and collagen. The pores of this material, initially very small, gradually

become larger as the collagen, a normal protein constituent of the body, is slowly absorbed.

Other research has been concerned with physiological factors underlying certain of the complications that may arise during cardiovascular surgery and with the evaluation of drugs and procedures for coping with such surgical emergencies.

A serious complication of heart surgery is ventricular fibrillation, the uncoordinated contraction of the heart muscle resulting from derangements in the activity of its specialized conducting system. Although procaine amide is widely used to counter ventricular fibrillation, NHI studies suggest that the drug may do more harm than good. In addition to depressing heart output and blood pressure, the drug lowers the electrical threshold of the heart, rendering it more sensitive to the very factors initially responsible for the fibrillation.

However, xylocaine, widely used as a local anaesthetic, increases the electrical "tolerance" of the heart without adverse effects on heart contractility or blood pressure. The NHI scientists conclude it should be the drug of choice in such situations.

EXTRAMURAL PROGRAMS

Research Grants.....The National Heart Institute is supporting nearly 3,000 research projects through grants during 1963. The objective of this program is to stimulate and support research involving the study of the cardiovascular system and diseases which affect its function. Since heart disease is a complex of many different diseases, scientists must develop investigations in this area with a variety of approaches. Many studies supported by research grants are of a fundamental nature, exploring the basic structure and function of the cardiovascular system. Other studies, clinical in nature, deal with the application of the most recent developments in cardiac surgery or drug therapy in a specific area of cardiovascular disease. All of the approaches must be pursued and supported if we are to develop controls and ultimately prevent heart disease in man.

As a result of research efforts throughout the world, increased numbers of heart disease victims are able to anticipate complete recovery and a more productive life. This has been possible due to the information being made available on (1) disorders in the structure and function of the cardiovascular system, (2) therapy of cardiovascular diseases by new chemical or surgical knowledge, (3) prophylactic measures which forestall onset of disease, and (4) control of disease entities for which there are not as yet available therapeutic means.

The following summaries represent only a few of the hundreds of findings reported in the scientific literature during the past year.

ATHEROSCLEROSIS AND CORONARY HEART DISEASE

Among the fatty substances believed to be causal factors in the development of atherosclerosis and coronary heart disease, cholesterol has been undisputed "king of the hill" for more than twenty years. The findings of countless experiments in laboratory animals and of many epidemiological studies in human populations have amassed a formidable body of evidence linking elevated levels of cholesterol in the blood to the development of the artery-clogging lesions of atherosclerosis.

There is also abundant evidence that the amounts and kinds of fat in the diet are important determinants of serum cholesterol levels. In general, serum cholesterol levels tend to be pushed up by diets high in calories and total fat, with the bulk of the fat calories derived from animal sources rich in cholesterol and saturated fats. Conversely, these levels tend to be reduced by diets containing less total fat, with the bulk of these fat calories derived from vegetable or marine sources rich in unsaturated fats.

Epidemiological studies indicate that most Americans habitually consume a diet hardly calculated to protect them against atherosclerosis. It is high in calories, total fat, and saturated fat. Many scientists feel that this diet is largely responsible for our present appalling mortality from heart disease. They believe that heart-disease mortality might be substantially reduced by modifying

this diet, and that these changes (which entail a substantial reduction in total dietary fat and the liberal substitution of unsaturated for saturated fats) need not cause a major upheaval in prevailing dietary habits nor make eating any less enjoyable.

In support of this contention, several limited, short-term studies on small population groups have shown the proposed type of diet to be generally effective in reducing serum cholesterol levels, simple enough to be prepared in the average kitchen, and palatable enough to encourage the great majority of the subjects to follow it faithfully throughout the period of study.

Still to be proved, however, is whether large numbers of Americans would voluntarily accept any basic modification in dietary habits for prolonged periods; and, if so, whether such modifications would appreciably reduce their heart-disease risk. To obtain such proof will require long-term population studies on a scale never before attempted.

Before such an ambitious project can be undertaken with any great prospect of success, its feasibility must be carefully tested. This is presently being done by means of a series of short-term studies in small groups of middle-aged American males. Three separate diets, differing in their content of saturated, polyunsaturated, and total fat calories, are being evaluated for their effects on various factors associated with increased heart-disease risk and also on the development of the disease itself.

Although successful in treating many cases of hypercholesterolemia, diet therapy has incurred enough failures to stimulate the search for drugs that might lower serum cholesterol levels by some direct action on processes involved in the absorption, synthesis, transport, or excretion of cholesterol.

Since most of the cholesterol of serum is derived, not from dietary sources, but from cholesterol synthesis by the liver, the current surge of interest in compounds able to block cholesterol synthesis is hardly surprising.

Of many inhibitors of cholesterol synthesis that have been tried thus far, only one--nicotinic acid (niacin)--appears to combine clinical effectiveness with low toxicity. Although the drug does produce side effects in some patients, these effects are seldom serious enough to necessitate discontinuing use of the drug. Used alone, nicotinic acid is generally effective in bringing about moderate reductions in serum cholesterol. It is even more effective when used in conjunction with cholesterol-lowering diets.

The fact that women enjoy a considerably greater degree of protection against coronary heart disease than do men has been appreciated for years. This protection appears to stem from estrogens (female sex hormones) secreted by the endocrine glands of women during their reproductive years. Many scientists have explored the use of estrogens to confer their "protection" on post-menopausal women or on middle-aged

males who were coronary prone or who had already suffered heart attacks. For the most part, these were short-term studies yielding inconclusive, often conflicting results. Many scientists felt that the protection (if any) conferred by estrogens was too dearly bought in view of the side effects frequently produced by the therapy: breast enlargement and loss of sexual drive in males, uterine bleeding in women.

Other studies conducted among middle-aged males who had previously experienced heart attacks, indicate that, while some degree of breast enlargement and loss of libido is to be expected with estrogen therapy, this price is not excessive in view of the protection afforded by these hormones. Reporting the results of this seven-year study, the scientists state that recurrent heart attacks were substantially reduced in the estrogen-treated group and that their five-year mortality was 50% lower than that of the control group who received only placebos.

The results of another long-term study suggest that estrogens may confer significant protection against heart disease in doses that produce no appreciable feminizing effects and no deleterious effects on libido. This study, too, was carried out among middle-aged males who had suffered heart attacks. In the estrogen-treated group, dosage was adjusted on an individual basis: low initial doses were gradually increased until the patient noted slight breast tenderness. He was subsequently maintained on this dosage unless increased side effects necessitated reducing it.

Three estrogen preparations were evaluated. Only one, consisting of mixed, conjugated equine estrogens, appreciably affected survival. However, this preparation performed impressively: during the first 18 months, heart-disease mortality in the group receiving this preparation was less than half that in the placebo group. Thereafter, the benefits were less spectacular, but still substantial: after three years, the mortality in this group was still 33% lower than in the placebo group.

These findings suggest that middle-aged males with overt coronary heart disease and perhaps those who are coronary prone might benefit substantially from estrogen therapy. Further, the protection conferred by these hormones need not necessarily entail intolerable side effects.

Most of the crippling and lethal effects of atherosclerosis result from the obstruction of vital blood channels by blood clots rather than by the atherosclerotic deposits themselves. The atherosclerotic lesion provides a roughened surface conducive to the formation of clots. Further, the high serum lipid levels usually associated with atherosclerosis appear to increase the clotting tendency of the blood and also to impede its clot-dissolving mechanisms.

These observations have spurred research along two promising approaches to the treatment of heart disease: anticoagulants, which reduce the clotting tendency of the blood, and fibrinolytic agents, which dissolve clots already formed--either by attacking the clot directly or by activating the body's own clot-lysing mechanisms.

The reports of earlier studies on the use of anticoagulants both as therapeutic and as prophylactic measures in coronary heart disease were almost unanimously favorable. The results indicated that anticoagulants reduced heart-muscle damage and substantially increased survival in heart-attack victims. Other results indicated that anticoagulants, used as a prophylactic measure, reduced the incidence of first heart attacks in patients with angina pectoris and substantially reduced the incidence of recurrent heart attacks among patients who had previously suffered myocardial infarctions.

In a number of recently reported studies, the benefits attending the use of anticoagulants in the treatment and prevention of heart attacks have been less spectacular. Some investigators have noted no significant differences in mortality rates between patients treated with anticoagulants and those who were not. Others have reported that anticoagulants appear generally ineffective at heading off first heart attacks in patients with angina pectoris and that the long-term use of anticoagulants neither increases long-term survival after first heart attacks nor significantly reduces the incidence of recurrent attacks.

Despite the controversy currently surrounding the use of anticoagulants, there is near-unanimous agreement on one point: more objective, carefully controlled studies are needed for the accurate assessment of the clinical value of both long-term and short-term anticoagulant therapy in coronary heart disease.

This controversy, at least as it pertains to anticoagulant therapy during the acute and convalescent phases of heart attacks, may be resolved upon completion of a collaborative study now in progress. The study, which involves 16 medical institutions and about 1,000 patients, is comparing two widely used anticoagulants, heparin and Warfarin. These drugs differ in their actions on the coagulation mechanism and also in their routes of administration: Warfarin is an oral anticoagulant, whereas heparin must be given by injection.

Even greater controversy surrounds the clinical value of fibrinolytic agents. These drugs cause the dissolution of blood clots, either by attacking them directly or by activating the body's own clot-lysing mechanisms. Probably the best of these agents currently available for clinical use is streptokinase, a bacterial enzyme prepared from streptococci. Streptokinase is an activator which promotes the conversion of a plasma protein, plasminogen, to plasmin, a protein-digesting enzyme that attacks the fibrin of blood clots.

Earlier studies with streptokinase were hampered by problems of purifying this enzyme--a serious problem that has been encountered with most fibrinolytic agents. Impurities not only make for variations in potency between different batches of the agent (hence for difficulties in determining proper dosage), but also increase the probability of undesirable side effects. Early streptokinase preparations were notorious for the high incidence of fever, chills, and other distressing

symptoms attending their use.

Although this problem has been largely overcome in the case of streptokinase, this drug poses still another problem. Streptokinase is an antigenic substance that provokes an antibody response. This makes the use of streptokinase in fibrinolytic therapy strictly a one-shot approach, since its repeated use may cause severe immunologic reactions.

Urokinase, an activator found in human urine, should not pose such problems (on theoretical grounds, at least) since it is a "native" protein. It should be a better fibrinolytic agent than streptokinase if it can be prepared in a suitably purified form.

In recent years, many investigators have used fibrinolytic agents against various thromboembolic disorders, including thromboembolic complications of coronary heart disease. A number have reported moderate to marked clinical success with these drugs. However, present techniques for evaluating the effectiveness of fibrinolytic agents leave much to be desired; and, as a result, case reports have tended to lean heavily upon the patient's subjective response and on the investigator's clinical impressions. Most thromboembolic disorders are notorious for their unpredictable clinical courses; hence such studies have been of only limited value in assessing the value of fibrinolytic agents in the treatment of coronary heart disease.

The concept that the dynamic mechanisms of the blood system can be harnessed for enzyme therapy in coronary heart disease in an exciting one. Perfection of fibrinolytic therapy would open a new era in the treatment of thromboembolic disorders and perhaps give the practicing physician his greatest weapon toward cutting the mounting death rate from heart disease. However, despite glowing accounts of the accomplishments and potentials of enzyme therapy, the present state of fibrinolytic treatment leaves much to be desired. There are tremendous gaps in fundamental knowledge of the mode of action of fibrinolytic activating agents and difficulties in isolating and purifying these agents and estimating their potency. Moreover, proper evaluation of claims of successful therapy in relatively large groups of patients awaits more carefully controlled clinical studies. Until some of these problems are overcome, this rapidly expanding field is likely to remain a highly controversial one.

Electrocardiograms often reveal heart disease which other diagnostic techniques may fail to detect. Yet this valuable diagnostic tool is often impractical for large-scale population studies because of the high cost in time and money of conventional multiple-lead electrocardiograms. Earlier attempts to get around this problem by using fewer leads were generally unsuccessful because of losses in diagnostic sensitivity.

However, scientists in Oklahoma City have developed and tested a simple, rapid, and highly specific technique that may overcome these

problems. The electrocardiogram is taken by means of a single, oblique chest lead which records potential differences between two electrodes: one placed on the right side of the chest just below the collarbone, the other on the back about three fingerbreadths below the tip of the left shoulderblade. The electrodes are mounted in a plastic halter that is easily slipped into place without requiring that the subject undress. As many as 50 subjects per hour can be screened by this method.

The oblique chest lead was effective in demonstrating myocardial infarction, left ventricular enlargement, arrhythmias, atrioventricular and bundle branch block, and other heart abnormalities. This abbreviated method was 87% as accurate as conventional multiple-lead techniques in 996 subjects; and, with further experience, a sensitivity of 90% was obtained.

Although the technique was tested primarily to determine its usefulness in screening large populations, the investigators feel that it might also prove valuable for annual or periodic industrial employee health check-ups, for screening school children, and for obtaining electrocardiograms during exercise. The tracings obtained might also lend themselves well to rapid computer analysis.

An assisted-circulation technique called synchronized arterial counterpulsation is currently being employed to provide circulatory support during the acute stages of heart attacks or during heart

failure. The technique substantially reduces the work load of the heart while maintaining, or even increasing, coronary and systemic bloodflow.

In this technique, one cannula is placed in the abdominal aorta, another in the femoral artery. These are connected in a loop circuit with a two-way pump. The pump, which is activated by an electrocardiograph, aspirates a given volume of blood from the aorta as the left ventricle contracts. This reduces aortic pressure, decreasing the resistance against which the ventricle must eject blood, thus reducing left ventricular work.

When the ventricle relaxes and the aortic valve closes, the pump returns the same volume of blood into the femoral artery. This raises aortic pressure, hence coronary perfusion pressure, at the time when these arteries receive the major share of their blood supply.

Now being tested clinically, counterpulsation might well prove lifesaving in many instances of heart failure or heart attacks, providing assistance to the heart until it is once again able to assume its circulatory duties. Other evidence indicates that the technique may also confer long-term benefit to heart-attack victims by stimulating the development of collateral blood channels in the heart.

RHEUMATIC HEART DISEASE

During the past ten years, the death rate from rheumatic heart disease has dropped by 28%. This decline is due in large measure to three factors: increased awareness that rheumatic fever can be prevented by the prompt diagnosis and adequate treatment of infections due to group A beta hemolytic streptococci; the more vigorous use of continuous penicillin prophylaxis in rheumatic-fever victims to prevent heart-damaging recurrences; and improved surgical techniques for the repair or replacement of heart valves damaged by rheumatic heart disease.

At present, the main hope for eradicating rheumatic heart disease as a significant cause of death lies in the prevention of rheumatic fever. How rheumatic fever works its mischief in the heart and why it attacks some hearts and spares others remain largely unanswered questions. If the capricious disease should strike at the heart, medical science can do little either to prevent its onslaught or even to reduce the severity of that onslaught.

Fortunately, rheumatic fever is preventable. It seldom occurs if the precipitating strep infection is promptly and adequately treated. Recurrences can usually be prevented by continuous antibiotic prophylaxis in people who have already suffered rheumatic fever attacks.

Formerly, effective rheumatic-fever prevention was hampered by the slow, cumbersome means available for identifying group A beta hemolytic streptococci. Today, this obstacle has been largely overcome by

the fluorescent antibody technique. This technique, which has repeatedly proved its worth in field trials, makes it possible to identify these germs in only three hours. Earlier techniques had required three days or more. By reducing the time required for accurate diagnosis, the new technique makes possible the rapid initiation of antibiotic therapy in strep infections and thus minimizes the danger that rheumatic fever may subsequently develop. At present, the Heart Disease Control Program is conducting a vigorous training program to familiarize personnel of State and local health departments with the technique to insure its widest possible application.

The strides made in techniques of preventing rheumatic fever have also been matched by strides in surgery to mend hearts whose valves have been scarred or deformed by rheumatic heart disease. In many cases, improved techniques of open-heart surgery make possible the repair or reconstruction of even severely damaged mitral or aortic valves; and, if the valve is too far gone to be repaired, it can often be completely replaced by ingenious artificial valves. And, though such operations are far from routine and the operative risk still substantial, the patient's chances of cure keep improving all the time.

HYPERTENSION

The National Heart Institute conducts and supports a large body of research on hypertension and on the evaluation of drugs for treating it. In addition to assessing the clinical effectiveness of such drugs, these studies also explore the mechanisms by which such drugs affect blood

pressure. Such knowledge might provide valuable leads to the development of more effective drugs. It might also provide important clues to the underlying causes of hypertension.

Biochemically, the victim of essential hypertension is distressingly similar to his more fortunate fellows who do not have this puzzling disorder. Scientists have searched for years, but have found no substance in the blood or tissues of hypertensive patients that might be blamed for their elevated blood pressure. Other factors suspected of playing some nefarious role in hypertension: an upward reset of the central nervous system barostat to stabilize blood pressure at excessively high levels; a genetic trait; hormonal or enzyme factor affecting the production and/or metabolism of certain amines; and primary kidney disease. All are suspected, but thus far none of them has been convicted.

Although the causes of essential hypertension remain obscure, the physician today has at his disposal a fairly wide selection of drugs that effectively control blood pressure in hypertensive patients. Two promising new drugs, described in some detail elsewhere in this report, have been added to his armamentarium only this year.

Some forms of hypertension arise from clots or atherosclerotic deposits obstructing bloodflow to the kidney. The kidney responds to an inadequate blood supply by releasing renin. In the blood, renin catalyzes the formation of angiotensin, a powerful blood-vessel constrictor. Hypertension of renal origin is believed to account for 20-25% of all cases of hypertension.

Many cases of hypertension arising from renal artery obstruction can be cured by restoring normal bloodflow to the affected kidney. This is usually done by surgery to remove the obstruction or else to bypass it with a synthetic blood-vessel graft. Unfortunately, not all patients can be benefited by surgical treatment, and a careful diagnostic workup is required in selecting candidates for surgery. However, among those patients selected to undergo surgery, cure rates as high as 90% have been achieved by some surgical teams.

CONGENITAL HEART DISEASE

Estimates of the incidence of congenital heart disease range from 2 or 3 cases per 1,000 live births up to 7 per 1,000. Of those cases not detected and treated surgically, about 34% die during the first month of life, and 61% die within the first year. Most of these infants can be saved, thanks to spectacular advances in diagnostic and surgical techniques made over recent years.

An area of research in which NHI scientists and grantees have made substantial contributions is concerned with the development of improved techniques for diagnosing and evaluating congenital or acquired heart defects. These techniques assist the cardiologist in determining 1) whether such a defect exists, 2) where it is located in the heart, 3) how serious it is, and 4) whether it can be corrected or improved by surgery. If the defect can be corrected, this information assists the surgical team in planning its procedures so as to provide maximum benefit to the patient while minimizing his risk.

One of the most versatile and useful tools available to the cardiologist has been around for many years. It is a long slender piece of plastic tubing called the cardiac catheter. This tubing is introduced into the heart via a suitable blood vessel. Through this piece of tubing, blood samples can be withdrawn for analysis; blood pressures can be measured within the heart chambers; radiopaque substances can be introduced for X-ray visualization of the heart and great vessels; and dyes

or radioactive substances can be injected to measure heart output, to detect faulty heart valves, or to detect abnormal openings in the muscular wall (septum) that divides the heart into two pumping systems.

Several new techniques developed by NHI scientists or grantees have proved to be highly reliable, sensitive means for detecting, localizing, and estimating the magnitude of cardiac shunts.

A cardiac shunt is the flow of blood through abnormal openings in the muscular wall separating the left and right sides of the heart. Shunts can be caused by a number of congenital defects, and are one of the most commonly encountered signs of congenital heart disease. Most can be corrected by surgery. The operative risk is low and the chances of success excellent if the shunt can be diagnosed and corrected before it causes irreversible damage to the heart or pulmonary blood vessels.

One technique developed by NHI grantees for the pin-pointing of cardiac shunts and for measuring myocardial bloodflow employs a newly available radioactive isotope, rubidium-84. The decay of this isotope leads to the simultaneous emission of two gamma rays traveling in exactly opposite directions. These gamma rays are detected by means of sodium iodide crystals, placed on opposite sides of the heart and facing one another. They are counted only if both iodide crystals are struck simultaneously. This coincidence counting technique makes it possible to scan very small areas of the heart to measure blood flow and direction or to detect heart defects.

Once the heart defect has been detected, evaluated, and found to be amenable to surgery, the surgical team can undertake the repair or amelioration of the defect with surprisingly good prospects of success.

One surgical team recently reported their experience with 400 cases of congenital heart disease in infants less than two years old. Sixty percent of these infants were less than six months old. The operations were performed for a variety of congenital defects: some relatively simple, others exceedingly complex.

The overall survival rate was 72%, or 288 of the 400 patients. Mortality varied with the complexity of the malformation, and was highest among infants with multiple anomalies.

During the period of this study, 154 infants were found to have congenital heart disease at autopsy. The congenital defects found in 70 of these infants could probably have been corrected or improved by surgery had they been detected.

The high salvage rate in surgically treated infants, when compared with the high mortality in untreated similar cases, emphasizes the need for an even more aggressive effort toward early diagnosis and treatment of congenital heart disease, the authors conclude.

CARDIOVASCULAR SURGERY

Ingenious techniques for repairing certain heart defects were developed during the 1940's and 1950's. However, the application of these techniques could be likened to repairing a water pump while it is still running: the surgeon had to work by feel alone in an operative field that squirmed and pulsated with each heartbeat.

Before they could undertake the correction of any but the simplest heart defects, surgeons had to learn how to sustain life during direct-vision surgery in widely opened, stilled hearts. The development of two such life-support techniques, hypothermia and extracorporeal circulation, has not only made such surgery possible, but has also paced most of the progress in this field.

Hypothermia, or total body cooling, slows body metabolism and reduces the oxygen requirements of the tissues, so that the heart and brain can tolerate short periods of interrupted bloodflow.

Even more time can be gained within the stilled, non-functioning heart by using extracorporeal circulation. In this technique, blood bypasses the heart and lung completely. It is pumped and oxygenated by a heart-lung machine located outside the body.

Although each of the several types of heart-lung machines developed during recent years has its own particular advantages and disadvantages, all of those in clinical use are adequate for most cardiovascular surgery. The type of heart-lung machine employed is considerably less

important than the surgeon's skill and familiarity with the equipment in determining the success or failure of an open-heart operation.

Once hypothermia and extracorporeal circulation had demonstrated their individual worth in cardiovascular surgery, surgeons capitalized on the advantages of both; the combination of hypothermia with low-flow heart-lung machines provided the surgeon with direct-vision access to the stilled heart for periods long enough to correct even the most complicated defects.

An ingenious innovation was the incorporation of a heat exchanger into the heart-lung circuit to induce hypothermia by direct cooling of the blood. This technique is far more efficient in reducing the oxygen needs of the patient than is immersion hypothermia because those tissues requiring the most oxygen, hence the greatest blood flow, will be cooled most rapidly.

Recent Developments In Instrumentation. A new, simplified heat exchanger recently developed by NHI grantees consists of two stainless steel sheets, which are separated by a thin gasket to form a single, flattened blood channel. As the blood flows through this channel, it is cooled by cold water circulated through the surrounding water jacket. The unit is inexpensive, easily cleaned and assembled, and requires only a small volume of blood for priming. More important, it eliminates the hazard of internal leaks and minimizes damage to blood components. The capacity of this system can be readily increased simply by arranging individual units in parallel.

Several groups of NHI grantees have been investigating selective hypothermia during heart-lung bypass. In this technique, profound hypothermia is induced in the heart by direct cooling while the rest of the body is cooled only moderately or not at all. The heart is chilled by applying saline slush directly to the heart surface, by irrigating the membranous sac (pericardium) surrounding the heart with cold saline, and/or by perfusing the coronary arteries with cold, oxygenated blood. Experimental and clinical studies have shown that selective hypothermia is safe and effective, permitting the heart to be stopped for periods of ~~one~~ hour or longer.

The procurement of the large quantities of blood ordinarily needed to prime the heart-lung machine has frequently posed problems in scheduling open-heart operations. Much of this blood can be replaced with low-molecular-weight dextran, according to recent findings by NHI grantees. The use of this plasma expander not only simplifies blood-procurement problems, but also gives superior clinical results. Low-molecular-weight dextran prevents the aggregation of red blood cells (sludging) during heart-lung bypass, reduces the likelihood of transfusion complications, and decreases blood-cell destruction.

Another method recently reported by NHI grantees completely eliminates the need for blood to prime the heart-lung machine. A 5% solution of dextrose is used instead. Perfusion is carried out under normothermic conditions, using a disposable plastic oxygenator. The method is convenient, increasing the availability of heart-lung bypass

as an emergency procedure. It also conserves the patient's own blood volume and permits operations on patients who have religious objections to blood transfusion.

Reciprocating piston-type blood pumps have an advantage over roller pumps in that they permit adjustments in the volume of blood ejected with each pumping stroke. However, their usefulness has been limited because of the excessive destruction of blood cells trapped between the piston and cylinder wall of such pumps. A new pump of this type uses a piston considerably smaller than the cylinder. Acting as a seal between piston and cylinder is a "rolling diaphragm" of silastic and dacron mesh that practically eliminates damage to blood cells. There was no visible hemolysis after the pump had been used for nearly 10 hours in a patient suffering from heart failure.

Membrane oxygenators, which shield blood from direct contact with the oxygenating atmosphere, reduce the potential hazards of hemolysis, protein denaturation, and embolus formation. However, until recently, they were bulky, inefficient at high rates of bloodflow, and required large amounts of blood for priming.

The problem was that the film of blood, flowing linearly between two membranes, became fully oxygenated adjacent to each membrane but not in the center of the flow. Through-and-through oxygenation of the blood film could be achieved by decreasing its thickness, but this would require a large increase in membrane surface-area. NHI grantees

have solved this problem by using teflon support mats with multiple conical projections between each unit of the membrane "lung". The conical points "dimple" each membrane from the outside, disrupting the stream-lined flow of blood, increasing blood agitation, and thus insuring complete oxygenation. The new support mats, which will soon be in mass production, make possible a 50% reduction in the size of membrane lungs and the use of thicker, less fragile membranes.

Prosthetic Devices. The development of cardiovascular prostheses--artificial blood vessels, heart valves, patches, and plugs made from synthetic materials--has progressed sufficiently to make possible the repair of many acquired and inborn defects of the circulatory system in humans. The replacement or bypass of diseased and damaged arteries with synthetic textile tubes has saved approximately ten thousand lives. Severely damaged aortic or mitral valves have been replaced by prosthetic valves installed at the site of the natural valve in patients. Other valve types are being tested in animals. And, research is progressing toward the day when irreparably damaged human hearts can be totally replaced by small mechanical pumps implanted within the chest. Several prototype prosthetic hearts have already undergone preliminary trials in dogs.

Heart Valves. Valves for intracardiac use pose many problems in design, construction, and insertion. To be successful, such a valve

must: 1) close quickly in response to backward flow of blood without inhibiting forward flow; 2) be constructed of materials that neither affect, nor are affected by, blood and tissue, and that retain their intrinsic qualities of strength and elasticity for years of constant use in such an environment; 3) be securely anchored in tissue that writhes and twists with each heartbeat; 4) not restrict normal dilation or contraction of heart chambers; and 5) in the case of aortic valves, not block the flow of blood into the coronary arteries which originate at the level of this valve.

That these problems are not insurmountable is indicated by the successful clinical results obtained with several different types of prostheses in replacing diseased heart valves.

Aortic valves have been replaced with flap valves, bi- or tricuspid valves, or ball valves fashioned from various substances and installed at the site of the natural valve. Materials used, alone or in combination, include Teflon, Dacron, silastic, polyurethane, polyvinyl, and stainless steel.

Although prosthetic aortic valves are still in various stages of experimental development, and the operations for their insertion are still far from "routine", their use is not limited to patients in the terminal stages of disease.

Recently reported results with one type of valve, inserted in a

total of 90 patients aged 6 to 63 years, showed an over-all operative mortality of 16% (15 patients). Of various factors that, alone or in combination, were responsible for these deaths, most are preventable. This indicates that the mortality rate should be significantly reduced in the future.

NHI grantees have reported limited clinical successes with artificial mitral valves. These include flexible monocuspid and bicuspid valves and ball valves, constructed from a variety of materials. Many of these valves, including one currently under development in the NHI Surgery Branch, are anatomically very similar to the normal mitral valve.

Mitral and aortic valves developed by Dr. George J. Magovern and Edward M. Kent, of the University of Pittsburgh School of Medicine, contain curved stainless steel pins that, upon valve insertion, are mechanically ejected into the surrounding tissue and locked into place by a catchspring. The pins thus eliminate the use of sutures that may engender blood clots, and greatly reduce the time required to fix a valve into place. The valves had performed satisfactorily in 4 patients for periods of up to 5 months postoperatively, at the time of the scientists' report.

Prosthetic Hearts. The proven practicality of blood pumps for heart-lung machines and of artificial blood vessels, valves and other substitute parts for the heart has led many workers to believe that miniature blood pumps may be designed for installation within the body. These workers envision a prosthetic heart--complete with inflow and outflow tracts, valves, and pumping chambers--for the total and permanent replacement of irreparably damaged human hearts.

Research toward this goal has already commenced in several research institutions in the United States. To date, no fewer than eight types of artificial hearts have undergone preliminary trials (for periods of up to 21 hours) in dogs, and others are in earlier stages of development. These devices, however, are not sufficiently developed to warrant their installation in humans. Most of the research on prosthetic hearts is aided by NHI grant funds. For example, NHI grant-supported work at the Cleveland Clinic Foundation, by Dr. Willem J. Kolff and co-workers, has resulted in the development and preliminary testing of several prosthetic heart prototypes. Another grantee, Dr. B. K. Kusserow of the University of Vermont College of Medicine, designed a mechanical heart that functioned for one to two days as a partial substitute for the living heart in dogs.

Training Grants and Fellowships. The National Heart Institute is supporting over 800 training grants, fellowships, and research career awards. These awards were made through the NHI program that provides for the training of qualified persons for research and academic careers in basic and clinical sciences related to cardiovascular health and disease.

The Heart Institute awarded $11,296,000 for 343 training grants, $3,185,000 for 431 research fellowships, and $1,221,000 for 69 research career awards.

The training program of the National Heart Institute has the dual objectives of (1) improving the quality of both basic and clinical research training in fields concerned with the study, prevention, and treatment of cardiovascular disease, and (2) attracting promising young students to careers in medical research in order to increase the national supply of cardiovascular scientists, teachers, and highly trained physicians. Training programs are supported at the medical undergraduate level, the graduate level and at various levels where training is important to the production of future medical research scientists in the cardiovascular field.

The undergraduate training program provides support for schools of medicine, osteopathy, and public health for the purpose of improving the instruction in subjects related to the cause, recognition, and management of cardiovascular disease. With this additional support, the

schools are able to develop well-staffed and well-equipped training programs. As a direct consequence, the physician-graduate of today has received a much more thorough training in the fundamental basis of disease, as well as better methods of diagnosis and treatment, than earlier graduates. Through this program the medical schools have not only raised the standard of competence of the profession as a whole, but have also encouraged a larger number of physicians to seek more advanced training and experience. The undergraduate training program has also made possible the stimulation and strengthening of cardiovascular research in the schools, and has enabled the schools to provide more comprehensive and intensive training in the clinical and public health aspects of cardiovascular disease. Many more medical students have become interested in medical research since it has been made possible for them to participate in the research activities of their schools. These beneficial effects of the undergraduate training grants will continue to be in force in the schools.

Graduate training grants support special training programs in basic and clinical cardiovascular research areas in medical schools, universities, and other training institutions. The grants, handled locally by the program directors, cover certain costs of training and research and pay stipends to qualified candidates selected by the institution. They help to provide greater stability to meritorious training programs in various basic and clinical disciplines in the cardiovascular field and serve as a stimulus to research interests and activities of

young medical scientists in the university and medical school environment. This type of grant is an effective means of producing additional research personnel in areas of manpower shortage. In addition to reducing the primary manpower shortage, these programs aid in bringing the basic and clinical scientists together in broader study of cardiovascular diseases through training involving multiple disciplines and several departments. Training programs are utilized to establish instruction in new or undeveloped disciplines to take advantage of unusual opportunities and new approaches.

The fellowships program supports research training of qualified scholars for research and academic careers in the basic and clinical sciences related to the cardiovascular area.

Special fellowships support the advanced training of qualified applicants whose needs make other types of fellowship support inapplicable.

The research career award program was created to increase stable full-time career opportunities forscientists of superior potential and capability in the sciences related to cardiovascular areas.

Two types of awards are available: career awards and developmental awards. Career awards help institutions to recruit and keep highly skilled investigators of proved competence and scientific merit. Developmental awards enable institutions to finance positions for

qualified scientists who have 3 years or more of relevant postdoctoral research or professional experience.

The training grants and research fellowships programs of NHI are helping substantially to add to the nation's resources for heart research; and these programs, year by year, demonstrate that they constitute an indispensable component of the Institute's activities and one without which continuing growth and development in the progress of heart research itself could not be attained.

COLLABORATIVE STUDIES PROGRAM

The need for a collaborative studies branch in the NHI arose from the abstruse nature of the cardiovascular disease problem. Traditionally, medical research is conducted in medical centers, universities, and hospitals, where scientists pursue especial research interests either through the care of patients, or through the use of laboratory animals or test tubes in experimental situations. However, through development of modern statistical methods and data processing and analysis, newer fields of scientific investigation leave the traditional environs of ward and bench to study the "grass-roots" circumstances under which a disease develops or flourishes in given communities and attempt to capitalize on what is called "experiments of opportunity." In these "experiments," nature or some fortuitous circumstance has contrived to isolate factors in a population or its environment that may be studied for their impact on the development of cardiovascular disease. In addition, standardization of modern methods and equipment has now made it possible for investigators working at far-flung corners of the earth to pool their separately collected data and build hypotheses which the individual workers would never have been able to develop alone.

Epidemiological studies are particularly valuable for testing hypotheses concerning causal factors in atherosclerosis and coronary heart disease. Although these studies may not be able to prove that this or that factor is a definite cause of coronary heart disease, they are frequently able to establish consistent associations between some factor and the development of disease and to determine the magnitude of the risk attending its

presence. These associations provide valuable leads for intensive followup in the laboratory.

Epidemiological studies have forged strong links between the development of coronary heart disease and a number of factors. These include age; sex; diet; over-weight; metabolic disorders, such as hypothyroidism, hypercholesterolemia, and diabetes; elevated blood pressure; cigarette smoking; occupation and degree of physical activity; psychic stress; geographical location; and others.

The complex interplay of this imposing constellation of factors poses problems for the epidemiologist attempting to assess the contribution of some single factor such as diet. However, he is frequently able to isolate this factor by comparative studies on population groups which differ widely with respect to the prevalence or severity of coronary heart disease, but which are as similar as possible in all other respects except for dietary factors which might account for the difference.

During the last fiscal year a concerted effort has been made to strengthen the existing programs of epidemiology, biometrics, and geographic pathology to fill major gaps in professional and laboratory resources for studies of heart disease in large populations. This effort has been made because of the promise of major contributions through such studies and also because of the interest and encouragement of the Congress toward a more vigorous program to examine dietary and geographic factors of coronary heart disease. The Congress has pointed out that, for example, contemporary attitudes concerning the hazards of animal fats in the diet are based more

on hypothesis than on sound scientific evidence. The House Committee on Appropriations noted that special difficulties involved in controlled population studies of various nutritional and cultural characteristics makes this area particularly suitable for broad collaborative efforts on an international scale.

Several significant research projects have been initiated or expanded within the United States and abroad under the collaborative studies activities during 1963. In addition to continuing research activities of programs carried out by the Framingham Heart Study, Framingham, Mass., the Biometrics Research Branch, the Field Epidemiological Research Section, and the International Laboratories, the following activities have also been undertaken:

(1) A staff for clinical research trials has been organized to cooperate with grantees carrying out dietary feasibility studies and new studies of drug therapy in coronary heart disease.

(2) The Field Epidemiological Research Section has undertaken a follow-up study of approximately 25,000 former students at Harvard and the University of Pennsylvania from the years 1931-46 who received medical and psychometric examinations to determine whether precursors of coronary heart disease or hypertension can be identified. Initial data collection has proceeded satisfactorily.

(3) Collaborating investigators in England and Norway will obtain corresponding health information on relatives of immigrants to the United States remaining in those countries to compare morbidity and mortality information on chronic respiratory and cardiovascular disease

among those who came here and those who remained in their mother countries. Collection of this data has also proceeded satisfactorily. The rapid increase in chronic respiratory disease in the United States over the past two decades makes it particularly important to learn more about these diseases and their association with various forms of heart disease.

(4) Plans have been completed for a collaborative study to determine what factors account for the unusually low death rate from coronary heart disease among males, age 40 through 62 in Puerto Rico. Puerto Rican males of this age have only one-third the death rate from coronary heart disease of white males the same age in the continental United States. The death rate from coronary heart disease among Puerto Rican males who moved to New York City is midway between the island rate and that of other white males in New York. A major study of this "experiment of opportunity" is being initiated.

(5) Agreement on another epidemiological study of cardiovascular diseases has been reached between NHI and the University of Zagrab School of Public Health in Yugoslavia under PL 480. Again, investigators will be trying to take advantage of an experiment of opportunity created by differences in environment and ethnic patterns among population groups in that country.

RESULTS OF COLLABORATIVE PROJECTS

Most of the progress in collaborative areas has been made in studies conducted outside the continental United States. In general, Americans are

poor subjects for such studies since sectional differences in dietary patterns have largely vanished in the wake of general availability of foodstuffs through our excellent food distribution system.

Nevertheless, some experiments of opportunity do exist in this country. For example, currently underway is a study of diet and atherosclerosis in Benedictine and Trappist monks. The Trappists, largely vegetarians, eat eggs and dairy products, but no meat; the Benedictines are omnivorous. The evidence thus far indicates that the Trappists consume considerably less fat in proportion to their total caloric intake, have significantly lower serum cholesterol levels, and a lower prevalence of coronary heart disease than do the Benedictines. Similar studies are being undertaken among the predominantly vegetarian Seventh Day Adventists.

Today, Israel provides an especially fertile field for epidemiological studies. The influx of Jews from all parts of the world has localized within one small country population groups of widely different ethnic and geographic origin. Striking differences exist among certain of these groups, and equally striking differences in the prevalence and severity of coronary heart disease. Comparative studies of these groups provide unusual opportunities to assess the importance of genetic and environmental factors affecting susceptibility to disease, and to evaluate the impact of changing modes of life on the incidence of heart disease in these groups as they are assimilated into the Israeli culture. Israel also has at her command highly trained research manpower and the modern research facilities needed to exploit these opportunities.

Studies thus far indicate that coronary heart disease is much more common among Jews migrating to Israel from Western countries than among migrants from Asia Minor and Eastern countries. It appears to be especially rare among recent migrants from Yemen. Yemenites exhibit low serum cholesterol levels and a striking serum lipoprotein pattern that is said to be responsible for their freedom from coronary heart disease. These appear to stem from the Yemenite diet, which is very low in fat, especially saturated fat. Studies among Yemenites who have lived in Israel for eight years or more indicate that this characteristic serum lipid pattern is gradually lost with the adoption of more Westernized dietary patterns and modes of life.

Heart attacks are also extremely rare among semi-nomadic bedouins, who consume a diet high in carbohydrate, about average in protein, and low in fat, most of which is polyunsaturated. In view of the rarity of heart attacks, the prevalence of angina pectoris and hypertension in this population was surprisingly high, although considerably lower than among Western Jews.

Presently underway in Israel is a study of hypertension and coronary heart disease among 10,000 male Civil Service employees over 40 years old. The study population represents a cross-section on the various ethnic and demographic segments of the population of Israel. Examinations and gathering of data began in late 1962. Present plans call for continued observation of the population sample for five years, with re-examinations scheduled for 1965 and 1967.

The Japanese derive only about 10% of their total calories from fat, and their mortality rate from coronary heart disease is very low

(8.1% of all deaths vs. 34.5% in the U. S.). Autopsy studies comparing Japanese subjects with Americans from Boston revealed that the onset of coronary heart disease in Japanese subjects occurred about 20 years later than in American subjects and progressed thereafter at a much slower rate. The incidence of coronary heart disease in American subjects aged 20-30 was about as high as that in Japanese aged 50-60. No Bostonians more than 30 years old were found to be free of coronary heart disease; some Japanese remained free of the disease until their seventies.

An experiment of opportunity, arising as a result of radiation studies among survivors of the Hiroshima raid, may make possible a more accurate assessment of diet and other factors possibly responsible for the striking differences in coronary heart disease mortality between Japanese and Americans. One of the byproducts of the radiation study has been excellent data on the incidence and severity of cardiovascular disease in this population group. This study is making possible valid comparisons of coronary heart disease data from Hiroshima males with similar data from males enrolled in the Framingham study. These data should also prove extremely valuable in connection with epidemiological studies among the American Nisei and Japanese residents of Hawaii.

An important means by which the epidemiologist attempts to evaluate the influence of mode of life and environmental factors on the development of coronary heart disease is through studies comparing population groups in countries where coronary heart disease mortality is low with groups of the same racial stock who have migrated to other countries and have adopted, or are gradually adopting, different modes of life.

Such studies have shown that the Nisei, who have largely adopted Westernized ways of life, have about the same mortality from coronary heart disease as do other Americans. Hawaiian Japanese, who still retain many of their Oriental customs and dietary habits, have a coronary heart disease mortality rate higher than that of native Japanese, but much lower than that of the Nisei.

Similar studies are underway comparing a group of Italians who have migrated to Boston from Naples with a matched population of Neopolitans; Irish males who migrated to Boston with their brothers who remained in Ireland; and male Puerto Rican migrants to New York City with male residents of San Juan and with a group of white New York males.

THE FRAMINGHAM STUDY

In the United States, the Framingham Study represents the "microscopic" approach to the epidemiological study of coronary heart disease. This involves the intensive study of a relatively small group to detect within-group differences in the incidence of the disease and to discover factors within the host or his environment that appear to be responsible for these differences. These risk factors and their relative importance in the development of coronary heart disease are then assessed in long-term studies on subjects initially free from the disease. The aim is to determine whether the presence of one or more of these factors in members of the population significantly affects the subsequent development of the disease in these members.

The population under observation in Framingham is now providing increasing numbers of persons with cerebral vascular disease for epidemiological

study. Forty-two cases of cerebral thrombosis have now developed and can now be studied. Apparently, cholesterol is not a predictor of cerebral thrombosis as it is for coronary disease. Hypertension, however, is related to increased risk of cerebral thrombosis. The conversion of the collected data of 10 years from this study onto computer tape now makes possible analysis of cumulative observations and their relationship to the development of various heart disorders.

In addition, controlled studies on 5,128 adults for periods of 8-12 years indicate the following:

Age and Sex -- In both men and women, the incidence of coronary heart disease rises sharply with age. Men tend to develop the disease earlier than women, who enjoy about a 10-year lag in the development of angina pectoris and a 20-year lag in the development of heart attacks. Men also tend to develop more lethal forms of coronary heart disease.

Elevated Serum Cholesterol -- The risk of heart disease increases with elevations in serum cholesterol levels: the higher the serum cholesterol, the greater the risk. The effect of elevated serum cholesterol levels was greater in young men than in older men. In young men with serum cholesterol levels higher than 260 mg. percent the risk was approximately six times that of subjects whose levels were lower than 220 mg. percent, the average value for adult males at Framingham.

Elevated Blood Pressure -- In both men and women, there was a greater risk with increased blood pressure.

Electrocardiographic (ECG) Changes -- ECG changes not usually considered indicative of coronary heart disease nevertheless appear to identify

susceptible persons.

Cigarette Smoking -- Cigarette smoking more than doubled the risk of severer forms of coronary heart disease, such as myocardial infarction, but did not increase the risk of developing angina pectoris. Persons who smoked pipes or cigars appeared to run no greater risk than did non-smokers. A happy note was provided by the finding that persons who had given up smoking ran no greater risk than did those who had never smoked.

Obesity -- Men or women with weights 30% or more above the median weight for their height and sex double their risk of developing heart disease. The higher risk appears to be due primarily to elevations in blood pressure commonly associated with overweight.

Thus, through the collaborative projects technique research workers throughout the country and the world in the relatively new specialty of epidemiology have been able to gather valuable information about the physiology, the psychology, and the environment of persons who are particularly susceptible to heart diseases and then compare this data with that of others gathered about those who are less susceptible. In short, disease may now be studied from an additional perspective so that knowledge gained in this manner can be superimposed on that obtained by traditional patterns of study to give results which might never have been gained otherwise. This expansion of depth-in-field in medical research through greater cooperation among investigators has also led to the development of an improved administrative scheme to insure smooth operation of these projects which many times extend across international boundaries.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

The National Institute of Allergy and Infectious Diseases is the Federal agency chiefly responsible for the advancement of research on human disease caused by microorganisms (such as bacteria, rickettsiae, viruses, and fungi) and for the investigation of the widespread allergies (such as contact dermatitis, asthma, and hay fever). Included also within the field of interest is a variety of diseases of global importance (such as cholera, viral encephalitis, rabies, malaria, schistosomiasis, trypanosomiasis, and other diseases of parasitic origin). Since the world of microorganisms is so vast, and consequently the causes of microbiological disorder so numerous, the subject matter of concern to the Institute is exceptionally broad, and the program of research is carried on both intramurally and extramurally.

Considered as the direct descendent of the first Public Health Service installation, the National Institute of Allergy and Infectious Diseases is the oldest of the National Institutes of Health, having observed its 75th anniversary only last November (1962). It stems from the year 1887, when the now-famous Dr. Joseph J. Kinyoun established at the Marine Hospital on Staten Island a one-room "hygienic laboratory," mostly for the investigation of the communicable diseases then threatening the United States as a problem arising through immigration. Moved to Washington in 1891, the Hygienic Laboratory became in 1930 the original National Institute of Health. The

immediate forerunner of NIAID was the National Microbiological Institute, which was created in 1948 by regrouping a number of other existing laboratories.

Thus, the National Institute of Allergy and Infectious Diseases, while among the smaller of the National Institutes of Health in terms of men, money, and facilities, nevertheless remains as a cornerstone in the over-all structure of NIH. Since hypersensitive reaction and microbiological invasion together constitute the principal cause of human illness, and since microbiological agents are accessory to many categorical diseases for which sister Institutes bear names (cancer, heart disease, mental disorders, and so on), the work of NIAID traverses and supports the whole broad field of medical investigation. Today the Institute, operating under the legal authority of Sections 301, 431, and related provisions of the Public Health Service Act as amended (42 U.S.C. 241, 289a, et al.), has some 200 different research projects under active pursuit on the Bethesda campus and supervises the conduct of some 2000 grants in support of research at academic institutions.

While it is in general improper, if not impossible, to pigeonhole all of NIAID's subject fields into arbitrary groupings, as a matter of practical classification for administrative purposes the intramural work is now divided among nine laboratories: the Laboratories of Infectious Diseases, of Biology of Viruses, of

Immunology, of Bacterial Diseases, of Germfree Animal Research, of Parasite Chemotherapy, of Parasitic Diseases, of Tropical Virology, and of Clinical Investigation. Field stations in Hawaii, in Georgia, in the Panama Canal Zone, and at Hamilton, Montana, conduct special studies of auxiliary interest. Guidance in administration and in the supervision of the grants program is provided by an expert citizens' panel, the National Advisory Allergy and Infectious Diseases Council, made up of some 15 lay and professional consultants elected on the basis of a rotating membership.

The Program as a Whole

Although progress against the infectious diseases in recent years has been rapid and gains are continuing, serious problems remain unsolved even in the area of bacterial diseases where antibiotics have had so favorable an effect. The widespread allergic diseases, the extent of which has only recently come to be understood, constitute a whole field that can be expected to profit from modern techniques. New information about the basic processes which cause allergies may be broadly applicable to other diseases and abnormalities. Our knowledge of the viral diseases is still fragmentary in spite of impressive strides made in virology. Increased knowledge about the structure and functioning of viruses, the smallest "living" substances, is important for all the biological sciences. One of the challenges emerging from the study of

infectious and parasitic disease problems is a growing awareness among scientists and physicians of the relation of infection to chronic disorders. Future progress against many chronic ailments may be rooted in better understanding and more effective control of infections early in life.

In this broad context, the Institute program, intramural and extramural, is oriented partly toward the epidemiology, prevention, and treatment of infectious and parasitic diseases, partly toward the physiology and biochemistry of the infecting organisms and toward the changes initiated in the host by the infection, and partly toward investigations of the roles that infections and allergic factors may play in the production of chronic illness.

The Intramural Program

Laboratory of Infectious Diseases. The origins of the Laboratory of Infectious Diseases go back to 1887 when the Public Health Service bacteriology laboratory was established on Staten Island. Present-day research encompasses not only bacteria but viruses and fungi as causes of disease. In respiratory virus research, laboratory scientists have played key roles in the discovery of the first representatives of several viral groups (adenoviruses, parainfluenza, and respiratory syncytial viruses) now known to be responsible for a large percentage of the severe respiratory illnesses of children.

A major challenge to investigators of respiratory disease is delineation of still undefined viral causes of the illnesses.

The knowledge that about 60 percent of the more serious respiratory illnesses of young children can now be explained makes the development of effective preventive vaccines against the known agents a worthwhile undertaking. Several experimental vaccines have been tested, and additional vaccines will be prepared on a pilot study basis.

With colleagues of the National Cancer Institute, Laboratory scientists are investigating mouse polyoma cancer virus in the Laboratory in a natural urban environment and in a rural setting.

The program of the medical mycology unit of the Laboratory ranges broadly from basic laboratory studies of new and unusual fungi to the testing of experimental drugs for possible use in the severe fungal diseases for which there is presently no cure. One such study with the Laboratory of Clinical Investigation is later described in the section devoted to that Laboratory. The finding of the causative agent of histoplasmosis in urban Washington, D.C., is another notable accomplishment.

In addition to the team research projects exemplified above, the Laboratory supports basic research in medical and physiological bacteriology. This is a varied program devoted to the study of

fundamental biological activity of various bacteria, including the Staphylococcus and Streptococcus. Corollary studies on the biochemistry of antibiotics are a long-term interest of the bacteriologists.

In mid-1962 the Laboratory of Infectious Diseases established in Honolulu, Hawaii, the Pacific Research Section, a small group having as its specific objective the study of eosinophilic meningitis, which occurs in epidemic form in several important Pacific islands and which is presumed to be a parasitic infection acquired from local foods, possibly fish. Also under investigation in the Pacific area are certain viral diseases of particular importance to the 50th state.

Laboratory of Biology of Viruses. The Laboratory of Biology of Viruses is interested in viruses as infectious macromolecules capable of profound effects upon the metabolism of cells, rather than as the causes of infectious clinical diseases. Virus infection of a cell, replication of virus in the cell, and in some cases complete integration of the virus into the hereditary framework of the cell, make these agents very important tools for the study of fundamental cell processes. An additional advantage is the virus capability of self-replication, which makes it possible to demonstrate and identify a single ultra-small virus particle.

Most of the units making up this Laboratory are therefore investigating the biological and biochemical factors involved as a virus attaches to, enters into, multiplies in, and is released

from a cell. Cells of various origins grown in tissue culture and a variety of viruses are used in this work. Practical implications of basic findings may be tested in whole animals.

An important part of these basic studies concerns the biochemical and biophysical makeup of the virus itself. This requires mass production of large amounts of virus, with subsequent separation from impurities and fractionation of the purified virus into its various chemical components. Much current work is with the nucleic acids of viruses. The electron microscope is an important tool in studies of the physical structure of different viruses, since techniques are now available for the investigation of detailed substructure of individual virus particles.

Because of the intimate relationships between the virus and the normal metabolic processes of the cell it infects, several units of this Laboratory are investigating the biochemical, genetic, and morphological properties of normal mammalian cells as well as certain tumor cells. This information is essential to the eventual interpretation of the changes found as the result of virus infection.

Laboratory of Immunology. Since the activation of the Laboratory of Immunology in 1957, the research program has concentrated principally on basic studies. Recently there has been a tremendous resurgence of interest in the field of basic immunology. The

application of modern techniques of immunology to the study of human disease makes immunologic investigation a fruitful new research approach to many long-standing scientific problems. To supplement its highly basic laboratory research, the Laboratory of Immunology has initiated clinical studies in certain aspects of allergy and immunology. In collaboration with the Institute's Laboratory of Clinical Investigation, studies are being conducted on the immunologic aspects of such diseases as lupus erythematosus, nephritis, chronic thyroiditis, and others in which an autoimmune basis is suspected. As staff and patient material permit, other allergic and immunologic clinical problems will be considered.

Meanwhile, there continue in the laboratories studies on such problems as transplantation of tissues to observe host-versus-graft and graft-versus-host reactions during transfers of lymphoid cells, on antibody production and the mechanism of hypersensitivity, on autoantibodies in experimental animals, and on immunochemical and immunogenetic studies of the protein isoantigens in serum. In one facet of a broad study of cellular localization of antigens and antibodies, there has already emerged an application which may have far-reaching practical value in malaria eradication. In cooperation with the Laboratory of Parasite Chemotherapy, scientists used fluorescent antibody technique to demonstrate the parasite of human malaria, the first recorded instance in which a human malaria parasite has been seen by this method.

Other basic research which promises important practical information is a study of the chemical, physical, and skin-reactive properties of extracts of house dust, a substance to which nearly one third of all allergic individuals give a positive skin reaction.

The Laboratory of Bacterial Diseases. A major research effort of the Laboratory of Bacterial Diseases has to do with basic studies of intracellular parasitism. The investigation of this host-parasite relationship holds much promise of increasing our understanding of disease and immunity.

Specific research under way deals with possible changes in characteristics of infected, normal, and immune cells and the effect of the intracellular environment on the infecting organism. One aspect of this research is the investigation of antibody production by cells in vitro. Enzymatic and biochemical studies embrace the interrelationships of cells, microorganisms, and their products.

Studies on human and animal brucellosis are of long-term interest to the Laboratory. Effective medical treatment is now available for human cases, and a successful control program is reducing the incidence of bovine brucellosis in the United States. On a worldwide basis, however, human illness due to infection with Brucella is a problem of significant proportions, and economic losses as a result of the infection in domestic livestock have a tremendous impact on the agricultural economy. The Laboratory collaborates with the World

Health Organization and with other brucellosis research centers throughout the world on many problems in the field, including the classification of Brucella and the epidemiology of the disease.

Studies on the Staphylococcus are directed primarily toward determining the factors responsible for pathogenicity and toward development and standardization of tests for measuring the relative infectivity of different strains of the organism. Antigenic analysis as a tool for identification and classification is also receiving attention.

Other studies deal with Pseudomonas (which is emerging as an organism of considerable importance in debilitated, burned, and chronically ill patients) and with L forms of bacteria (which are of basic biologic significance).

Laboratory of Germfree Animal Research. As a reflection of the growing application and importance of studies of germfree animals, the Institute created a separate Laboratory of Germfree Animal Research in 1959. Since its inception, the Laboratory has continued to expand the scope of its research. Today, germfree guinea pigs, mice, chickens, and rats are being used in a variety of studies on immunologic and disease processes.

The purpose of research with germfree animals is to enable scientists to study problems uncomplicated by the presence of the microbial flora which "contaminate" all normal experimental animals.

Rearing such animals is one of the most demanding and complex methods employed in laboratory investigation. However, the resulting product, an animal completely free of detectable microorganisms, is itself a magnificent laboratory for the study of a multitude of biological problems.

Through cooperative projects with other Institute laboratories, as well as with different components outside the Institute, this technique is being brought to bear on problems in many areas of research.

The earliest work, using germfree guinea pigs, was a study of the role of intestinal bacteria in amebiasis, a parasitic disease. Recent findings from this continuing study are provocative. Relationships between the host, its normal flora, and other protozoan and worm parasites are being studied. Through the use of such "clean" animals, scientists are evaluating dietary factors in these infections.

Laboratory scientists are also turning their attention to the behavior of viruses in the germfree host. A comparison of the relative susceptibility of conventional and germfree mice as well as possible interactions among bacteria and viruses, are continuing interests of the staff.

Data gathered from a fundamental study of any differences between the conventional and germfree species can provide insight

into the ways that normal "contamination" may affect a host's physiology. Such unique scientific information has been essentially unobtainable until the advent of the relatively new specialty, germfree animal research.

Laboratory of Parasite Chemotherapy. The Laboratory of Parasite Chemotherapy has a large research investment in worldwide malaria eradication, a program to which the United States has a continuing commitment. As a direct result of a recent discovery by Laboratory personnel that it is possible to transmit monkey malaria to man, the whole problem of simian malarias is being restudied. Previously, malaria experts had taken for granted that simian malaria would not be a problem in the eradication of the human disease. Only one facet of the broad program of malaria investigation, the simian variety of the disease will continue to receive attention from the scientific staff, whose interests in malaria and other tropical diseases are many and varied.

As a result of the new finding--that simian malaria can be transmitted to man--existing projects have been strengthened by additional staff, and new projects have been instituted to explore the various ramifications of this global problem in the laboratory, the clinic, and the field. Human prisoner volunteers have contributed vital data concerning the clinical picture, as well as actual proof of the transmissibility of these malarias to man. A field unit in

Malaya, to remain for several years, will carry out, in an area of high infectivity, studies of all aspects of the simian-human malaria chain.

Another finding with interesting ramifications is scientific proof obtained recently that a strain of human malaria from South America is resistant to chloroquine, which has been used effectively since World War II, with no evidence of resistance. Continued emphasis is being given to fundamental aspects of other problems in tropical parasitology and chemotherapy. These include the chemotherapy of intestinal parasites, the effect of nutrition on chemotherapy, the resistance of parasites to drugs, intensive and extensive study of the development and chemotherapy of fixed tissue stages of certain mammalian malarias, and the culture of insect tissues.

The Section on Cytology, Laboratory of Parasite Chemotherapy, is located in Chamblee, Georgia. Since the spring of 1960, when two of the Section's staff members were accidentally infected with monkey malaria through the bite of an infected mosquito, a full-scale study of human infections has been under way with the help of prisoner volunteers from the Federal Penitentiary in nearby Atlanta. The Chamblee unit coordinates its malaria studies with those at the Bethesda laboratories and at the Middle America Research Unit in the Panama Canal Zone.

Laboratory of Parasitic Diseases. The Laboratory of Parasitic Diseases maintains a well-diversified research program with a strong emphasis on fundamental studies of parasites and parasitic diseases. The competencies and interests of the scientific staff cover the entire field of parasitology, such as the natural history of protozoa and helminths of medical importance, epidemiology of parasitic infections, immunity, and the physiology and biochemistry of parasites.

The primary interest of the staff is basic research, but laboratory data find application in the field and the clinic. Scientists of the Laboratory respond to requests for help and advice concerning practical problems on the prevention and control of parasitic infections. They are also consulted concerning the diagnosis and management of particular parasitic diseases. In recognition of these responsibilities, some activities of the staff are oriented to increasing the fundamental knowledge needed for solving such practical problems. Conversely, laboratory findings can stimulate clinical and field research.

An example of a field study which logically extends laboratory findings is a project in Puerto Rico on the relation of nutrition to helminthic infection. The project originated from laboratory data that showed beneficial effects of certain diets on infected animals. The principal infection under study is schistosomiasis, a debilitating illness affecting some 150 million people in tropical

and subtropical climates. However, observations are also made on concomitant infections with hookworms, whipworms, and stomach worms.

Research projects in progress include such diverse subjects as the role of helminths in the causation of cancer, the successful development of helminths and protozoa in germfree environments in animals and test tubes, destruction of snail carriers by chemical means, the fractionation of antigens, and the effects of nutrition on chemotherapy of parasitic diseases.

Laboratory of Tropical Virology. The Laboratory of Tropical Virology was established in 1959 to study viral infections transmitted by mosquitoes, mites, and other arthropods. These infections represent a significant proportion of the tropical diseases which the Institute has long emphasized.

In addition to its work in Bethesda, the Laboratory has a facility in Panama, the Middle America Research Unit, a joint effort of the United States Public Health Service and the Army. Originally a temporary field party, the Unit has filled the need for a tropical disease research laboratory physically located in the U.S. Canal Zone, but concerned with the health problems of tropical virology of the Institute; research on fungal diseases, particularly histoplasmosis, is supported by the Walter Reed Army Institute of Research.

The Bethesda-based laboratories and the Panama component work in close cooperation on mutual problems and, in addition, each has a research program essentially independent of the other.

A long-range project in Panama on the ecology of arthropod-borne viruses in a tropical rain forest is one of the collaborative studies on which the unit is working with scientists of the Gorgas Memorial Laboratory. Viruses isolated from mosquitoes and sandflies are characterized, identified, and studied to determine relationships to human or animal disease. In another study, an attempt is being made to explore the presently unknown role of chiggers and related arthropods of the American tropics in transmitting viral and rickettsial diseases to man.

In Bethesda, basic research is related to standardization of diagnostic reagents and to the pathogenesis and epidemiology of arthropod-borne and other tropical viruses, especially those in Middle America. Areas of special activity include studies of virus-vector relationships, of serological classification of virus strains, of pilot vaccines, and of laboratory techniques for isolation and diagnosis.

Laboratory of Clinical Investigation. The Laboratory of Clinical Investigation combines laboratory research with a program directly concerned with the study of patients admitted to the Clinical Center because of illnesses of special research interest to the Institute.

Since the first admission of patients in 1953, Laboratory physicians have accumulated some impressive, and in many instances unique, series of cases of hypogammaglobulinemia, cystic fibrosis of the pancreas, disseminated lupus erythematosus, and the systemic fungal infections. With both an inpatient and outpatient program, a large variety of projects are kept ready for activation to take advantage of unusual individual patients or groups of cases of infectious diseases which may occur unpredictably at any time.

A project of the Laboratory which hopefully will develop much needed information is a collaborative study with the Laboratory of Infectious Diseases on acute respiratory illnesses in patients. With the cooperation of human adult volunteers housed in the Clinical Center, it has been possible to produce, using respiratory syncytial virus, a rather uniform illness resembling a "cold." Volunteers have also participated in studies of primary atypical pneumonia and infections caused by parainfluenza viruses. These promising preliminary investigations form the base for long-term respiratory viral studies in patients.

The combined laboratory-clinic facilities have provided an opportunity to test new drugs in patients. One of these, a synthetic penicillin supplied by a commercial drug manufacturer, was given to a group of patients having a variety of severe staphylococcal and streptococcal infections unresponsive to conventional treatment. Concomitant biochemical studies in the laboratory produced basic information about

the structure and mode of action. Another drug, useful against the severe systemic fungal diseases, also was tested in patients. After earlier testing in experimental animals (by the Laboratory of Infectious Diseases) had shown promise, the drug was administered to patients seriously ill with various systemic fungal illnesses. Some of these responded dramatically to the new drug and thus provided hope that the new treatment will become a valuable addition to the limited means available for combatting these illnesses.

The Rocky Mountain Laboratory. The Rocky Mountain Laboratory was created in 1921 to study Rocky Mountain spotted fever, for which no preventive was known at that time. This special mission was completed when Laboratory scientists produced a vaccine effective against the disease. The vaccine, plus subsequent antibiotic treatment, has changed the nature of the problem over the years, but research interest in this and other arthropod- and animal-borne diseases continues.

Located in Hamilton, Montana, the Laboratory is a world center for study and control of diseases in Nature transmitted to man. Not only basic laboratory studies but their necessary corollary, field investigations, are under way on a wide selection of problems such as Q fever, tularemia, rabies, Colorado tick fever, and the arthropod-borne encephalitides.

Some of the long-term basic research in progress concerns the chemistry and synthesis of virus proteins and associated constituents,

mechanisms of allergic phenomena and their intriguing relationship to humoral immunity, prophylaxis of tuberculosis and salmonellosis, and studies of the fine structure of micro-organisms and the relationship of structural elements to biologic activity.

In spite of its relatively isolated location, the Rocky Mountain Laboratory attracts numerous professional visitors who wish to learn at firsthand its special methods and techniques, and to discuss ideas developed by the Laboratory staff. In a representative year 63 visitors, many from foreign countries, have made personal visits, and thus made possible a mutual exchange on the solution of varied problems.

The Extramural Program

In addition to the studies conducted by the National Institute of Allergy and Infectious Diseases in its own laboratories and clinical service, the Institute participates in three major extramural programs: research grants, training grants, and fellowships.

The research grants program supports investigations in universities, hospitals, laboratories, and other public or private institutions. Problems of health or disease broadly concerned with viruses, bacteria, parasites, fungi and rickettsia, as well as allergy-immunology, are eligible for grant funds. This support is intended to expand research activities and to encourage investigators and institutions to undertake original studies in neglected areas.

The Institute, through its research grants program, supports a number of projects in specific areas of tropical medicine. For the most part, support for research in the tropics has been requested for studies on transmissible diseases--primarily those that impose heavy economic burdens. These diseases include schistosomiasis, filariasis, malaria, Chagas' disease, and the arthropod-borne viral diseases. Other important diseases that are prevalent in the tropics and which receive substantial attention in research effort are tuberculosis, leprosy, cholera, and diarrheal diseases.

Diseases in the tropics constitute serious world health and economic problems. It is known that practically inexhaustible reservoirs of a number of transmissible diseases that have plagued mankind through the centuries in both temperate and tropic areas persist in the tropics and other underdeveloped areas. When climatic, host susceptability, and vector proliferation factors are favorable, the disease agents can quickly become established. There is no doubt that transmission is a continuous threat. Indeed, from what we know, we can only wonder why there are not more frequent and more serious outbreaks. Further, the tropical diseases impose a grave economic burden upon the developing countries. The potential benefits to be derived from the imaginative application of useful new concepts to the control or eradication of the major transmissible diseases will greatly outweigh the investment in effort and money.

Projects in the field of allergy-immunology that receive support range from clinical investigations on research patients to studies on the comparative development of immune mechanisms. Substantial progress is being made in identifying the components of and determining the interrelationship of anatomical structures and functions and autonomic control of the immune response. Very promising results have been obtained recently in applying new concepts derived from basic research (thymectomy, radiation, and use of cancer chemotherapeutic agents) to the transplantation of whole organs that would not be expected to succeed a year or so ago.

In recent years virological research capability in this country has been developed to a high order of efficiency and productivity. The findings of research in this area are comparable, in terms of complexity and achievement, to any other accomplishments by this generation of scientists. The investment in research in virology can be expected to pay off handsomely not only in the economic and health enhancing prospects but also in the development of new knowledge of biological phenomena at the subcellular level using viruses as an information transmitting and receiving probe.

At present, several kinds of bacterial diseases constitute continuing cause for concern in the United States. These are respiratory-tract infections by drug-resistant strains of streptococcus, diptheria and hemophilus organisms, urinary-tract infections that are especially

troublesome in women during their child-bearing years, in adolescent girls and in the aged; infant diarrhea, staphylococcal, and pseudomonas infections which have become difficult hospital management problems, and refactory tuberculosis resistant to streptomycin and isoniazid therapy.

Taken as a whole these diseases and a large number of lesser ones represent a continuing menace of sizeable proportions. Research is being supported across a broad front to enhance natural resistance factors, develop new antibiotics, and determine promising new avenues of attack on these persistent infectious bacterial problems.

We have been learning, however, that most pathogenic organisms, given the opportunity, can overcome the advantages we have been enjoying. Some general principles are now emerging from continued research in this area. One of these principles is that for each additional effective chemotherapeutic agent discovered the usefulness of all other antibiotics is extended because the number of possible combinations of all drugs available can be considered. A second important point is that hypersensitivity in some individuals to older drugs does not usually apply to new ones. Thirdly, each new effective agent invariably provides the scientist with an additional molecular probe with which to obtain new information on the processes of bacterial reproduction, toxin production, conversion to virulence, etc. Often the ability to control an opportunistic bacterial infection can make a remarkable difference in

ameliorating certain functional disorders, of which pyelonephritis and endocarditis are particularly noteworthy examples.

Training grants are awarded to institutions for the establishment or strengthening of programs designed to provide intensive training for research and academic careers in disciplines of importance to allergy, immunology and the infectious diseases.

Complementing the training program are fellowships at several different levels designed to provide support for orientation, indoctrination and participation in independent research and teaching, under the close supervision of sponsors recognized for their contributions to science.

In each category, funds are awarded only after the submission of formal applications reviewed by appropriate committees the members of which are selected for their eminence in the fields which they represent. Primary factors taken into consideration are scientific merit and potential significance of the proposed research, qualifications of the applicant, adequacy of facilities, and the appropriateness of the requested budget to the project described.

Over the years the research grants program of the Public Health Service has been evolving toward broader support of research. To implement this concept, the following grants are available in addition to the traditional grants for support of individual research projects. Program-Project grants are made to institutions, in the name of one or more

principal investigators, for the support of a broad-based and usually long-term program of research activity. Center grants are made to institutions solely for the support of physical resources (excluding new construction) and common services for broad and flexible research efforts usually, but not necessarily, clinically oriented.

Two groups of Research Career Awards are also available. The Research Career Award itself is intended to support additional stable positions for experienced investigators who are continuing to develop productive careers of independent research and teaching. The Research Career Development Award finances positions for able young scientists who plan to pursue careers in independent research and teaching.

A valuable facet of the research grants program is sponsorship of conferences on scientific subjects of high priority. Also grant-supported is a permanent Committee on Standardization of Allergens, which is presently concentrating on ragweed allergen reference standards, with a view to achieving a uniform product which can be used by investigators all over the country to combat the omnipresent ragweed, cause of perhaps the most widespread allergy afflicting the American people.

The Collaborative Program

At certain stages in research, whether intramural or extramural, continued development calls for the cooperative effort of academic institutions, private facilities, government, and industry. In the

National Institute of Allergy and Infectious Diseases, as in the National Institutes of Health as a whole, such activity, usually involving contractual arrangements as distinct from grant commitments, is known as "collaborative research." One of the most promising programs now (1963) under way in this area is the Vaccine Development Program, a venture aimed at producing suitable vaccines for defense against the major diseases of the upper respiratory tract (including the common "cold"). The success of the vaccine against Asian influenza in lessening the impact of this epidemic disease has encouraged research to develop new vaccines against other epidemic infections of the upper respiratory tract. Since the Vaccine Development Program was initiated in 1962, a number of contracts have been awarded to commercial firms for development of prototype vaccines. Other contracts are being negotiated for clinical evaluation of the new vaccines as they become available for testing. Small pilot lots of vaccine are first evaluated for potency and tested for purety and safety. After successful preliminary trials, controlled evaluation is extended through field trials. Work in collaboration with industrial research groups, universities, hospitals, and other facilities with potential for expansion in vaccine development and evaluation is now under way.

Another important activity of nationwide importance under the aegis of the Institute is the Virus Reagents Program. In the vital area of virology, the basic reagents used in critical experiments by hundreds of virologists generally have been put together in individual laboratories

with little assurance of comparability. The Institute has provided leadership for the collaborative Virus Reagents Program, under which many important types of viral antigens and antisera are being produced, stored, and distributed. These materials are essential to the identification of viruses and to an understanding of viral diseases.

Personnel

As of December 31, 1962, the National Institute of Allergy and Infectious Diseases had 653 full-time employees. Of the total, 255 were in professional and scientific positions with 249 in direct research and 6 in extramural activities; 238 were in sub-professional and technical support positions; 132 were in administrative and clerical positions; and 28 were in plant operation and maintenance. Among the doctorates held by the professional staff are M.D.'s, Ph.D.'s, Sc.D.'s, and D.V.M.'s. Medical and other scientific specialties represented include public health, epidemiology, microbiology, pharmacology, physiology, immunology, virology, dermatology, biochemistry, bacteriology, parasitology, zoology, entomology, mycology, malacology, and ecology.

Table 1 below presents a further breakdown of NIAID employment, according to program activity and pay system. Of the 653 full-time employees, 120 were Commissioned Officers of the Public Health Service, 432 were General Schedule employees in the Civil Service, 65 were Wage Board employees, and 36 were employees in the Panama Canal Zone.

TABLE 1

NIAID Employment by Pay System

LABORATORY OR ACTIVITY	C.O.	G.S.	W.B.	C.Z.	TOTAL PERM.
Scientific Planning and Direction	10	18	4	0	32
Laboratory of Infectious Diseases	22	78	4	0	104
Laboratory of Biology of Viruses	8	40	2	0	50
Laboratory of Bacterial Diseases	1	5	0	0	6
Laboratory of Parasite Chemotherapy	10	28	5	0	43
Laboratory of Parasitic Diseases	9	29	1	0	39
Laboratory of Germfree Animal Research	4	13	0	0	17
Laboratory of Tropical Virology	8	12	2	36	58
Bethesda	3	12	2	0	17
MARU	5	0	0	36	41
Laboratory of Immunology	4	21	2	0	27
Laboratory of Clinical Investigations	20	28	0	0	48
Subtotal	96	272	20	36	424
Rocky Mountain Laboratory	19	91	45	0	155
TOTAL RESEARCH	115	363	65	36	579
COLLABORATIVE STUDIES	1	11	0	0	12
Vaccine Development	0	6	0	0	6
Virus Reagents	1	5	0	0	6
Review & Approval	3	38	0	0	41
Administration	1	20	0	0	21
TOTAL NIAID	120	432	65	36	653

Budget

For fiscal year 1963, a total of $64,662,000 was available for all program activities of the National Institute of Allergy and Infectious Diseases. Funds for activities under the grants program, including research grants, fellowships, and training grants, amounted to $47,747,000. Direct operations, including research, collaborative studies, review and approval of grants, program direction, and the Rocky Mountain Laboratory facility, totaled $16,915,000. Table 2 below gives a summary of NIAID's total estimated budget for fiscal year 1963. Table 3 presents a breakdown of the budget estimate by major activity or field of research.

TABLE 2

Budget Summary by Program Activity
Fiscal Year 1963 Estimate
(In Thousands of Dollars)

Grants		
Research	$37,647	
Fellowships	2,900	
Training	7,200	
Subtotal Grants		47,747
Direct Operations		
Research	10,534	
Collaborative studies	5,029	
Review and approval of grants	857	
Program direction	403	
Rocky Mountain Laboratory facility	92	
Subtotal Direct Operations		16,915
Total All Activities		$64,662

TABLE 3

Budget Summary by Major Activity or Field of Research
Fiscal Year 1963 Estimate
(In Thousands of Dollars)

Grants

Research by Field:	Amount	
Allergy and Immunology - allergen standardization	$1,166	
Allergy and Immunology - all others	4,854	
Tropical medicine	9,027	
Vaccine (all types)	2,502	
Chronic bacterial diseases	4,666	
Viral respiratory diseases	2,088	
Enteroviral infections	884	
Other virology	3,292	
Others (genetics, cell biology, etc.)	4,617	
Additional indirect costs	501	
Subtotal		33,597
General research support grants	2,800	
Gorgas Memorial Laboratory	250	
Clinical research centers: categorical	1,000	
Subtotal		4,050
Subtotal Research		$37,647
Type of Fellowship:		
Postdoctoral	$ 906	
Special	530	
Research Career Award	1,464	
Subtotal Fellowships		2,900
Training Grants:		
Allergy and immunology	$2,015	
Tropical medicine and parasitology	1,641	
Infectious diseases	3,494	
Scientific evaluation of grants	50	
Subtotal Training Grants		7,200
Total Grants		$47,747

Direct Operations

Research:	Amount
Office of scientific director	$ 323
Infectious diseases	1,763
Biology of viruses	609
Bacterial diseases	123
Parasite chemotherapy	589
Parasitic diseases	417
Germfree animal research	184
Tropical virology	542
Immunology	289
Clinical investigation	657
Diseases of animals transmissible to man	1,417
Subtotal, research	6,913
Reimbursement to management fund	3,621
Total, research	$10,534
Collaborative Studies:	
Research reference reagents	3,157
Vaccine development	1,872
Total, collaborative studies	$5,029
Review and Approval of Grants:	
Regular program	394
Reimbursements to management fund	463
Total, Review and Approval of Grants	$ 857
Program Direction:	
Regular program	155
Reimbursement to management fund	248
Total, Program Direction	$ 403
Rocky Mountain Laboratory Facility:	92
Total, Direct Operations	$16,915
Grand Total	$64,662

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

The National Institute of Arthritis and Metabolic Diseases (NIAMD) was established by the 81st Congress. Authorized by Public Law 692, the Omnibus Medical Research Act, it was passed by the Congress on August 15, 1950. The action was taken in response to public demand. Many citizens, long aware of the terrible suffering and rising deaths due to the chronic diseases, and impressed in recent years by the progress of medical science, had been impatient with the slow rate at which these diseases were being brought under control. They believed correctly that more could be done, and more quickly, if generous financial support could be obtained for chronic disease studies.

Public demand had already led to the establishment of the National Cancer Institute, the National Institute of Mental Health, and the National Heart Institute. Similar action was responsible for the creation by the 81st Congress of the National Institute of Neurological Diseases and Blindness and the National Institute of Arthritis and Metabolic Diseases. The rapid progress made by the older Institutes in cancer, heart, and mental diseases amply justified the establishment and support of the two additions to the National Institutes of Health.

When the establishment of NIAMD was authorized, no funds were voted for its operation and maintenance. However, since early action

to correct this oversight was anticipated, the laboratories of the former Experimental Biology and Medicine Institute (EBMI), a previously non-categorical ("general") division of The National Institutes of Health (NIH), together with the budget of EBMI, were transferred to the new categorical National Institute of Arthritis and Metabolic Diseases. At the same time a National Advisory Council of six lay and six professional members was appointed, and some $600,000 was transferred from NIH funds for the Council's activities, enabling it to make a start in awarding research grants. In July 1951 some $800,000 of new money was provided for this purpose.

Some of the laboratories incorporated into the NIAMD trace back their origins seventy years or more. They have a proud record of accomplishment, in basic research, for example, and in areas of pain-killing compounds, and the lifesaving sulfa drugs; their elucidation of the nature of pellagra, a serious destroyer of health in the southern parts of the United States in the first three decades of this century, was the key to the elimination of this disease in this country.

Originally established for the study of the arthritic disorders and metabolic diseases, the Institute has continued to expand its activities to the point where it now conducts and supports research in a great variety of disorders, including diabetes and other metabolic diseases, thyroid disease, gastrointestinal disorders like

peptic ulcer and ulcerative colitis, cystic fibrosis, disorders of blood and bone and many others. In addition, and of equal importance, a great deal of basic research is carried on--fundamental studies in biochemistry, enzymology, physical biology, nutrition. The nature of the arthritic and metabolic diseases makes such studies vitally necessary, for there is still too little known about their fundamental cause and nature.

Both laboratory and clinical studies are performed at the Institute, with laboratory research running the gamut from studies of the molecular structure of hemoglobin to the development of special diets for control of certain metabolic diseases. For its clinical research the Institute shares the facilities of the Clinical Center with the other Institutes comprising NIH. In this area, specially selected patients with rheumatoid arthritis, gout, diabetes, and other diseases of interest to the Institute, participate in intensive research studies, studies designed to provide new facts about the cause of their disease.

Yearly appropriations from Congress enable the Institute to carry on its many activities, which are divided into two major areas: (1) The research conducted by the Institute's own scientists at Bethesda and elsewhere ("intramural and collaborative program"), and (2) the financial support of research and research training in the Nation's medical schools, universities, and other research centers.

The main objective of this "extramural program" is to expand research in non-Federal institutions by awarding grants-in-aid for selected research projects conducted by highly qualified scientists.

Thus, the NIAMD serves as a focal point for the national support of health research in its field and secondarily as an institution which itself conducts laboratory and clinical research aimed at discovering new knowledge about the prevention, diagnosis, and treatment of disease and disability.

Arthritis and Rheumatism

Several diseases are commonly grouped under the name of arthritis and rheumatism. They include (1) rheumatoid arthritis, which frequently leads to permanent crippling; (2) osteoarthritis, a joint disease of the aged--less debilitating but painful and frequently disabling; (3) rheumatic fever; (4) gout; (5) arthritis resulting from joint injuries or infections; and lastly, (6) a variety of rheumatic diseases in which muscles, tendons, tissues of the eyes, arteries, and other organs are affected. Depending on the tissues involved, these are designated myositis, iritis, periarteritis, among others.

Unlike cancer and several diseases of the cardiovascular system, arthritis and the metabolic diseases rarely lead to early death. They cause untold suffering, but the injury is to health and hence to the national economy. In terms of cost to the nation, these

diseases are much more serious than cancer and heart disease combined. Arthritis and rheumatism alone are conservatively estimated to cost the nation more than $1,000,000,000 annually. These figures are based on the estimate that 10 million people in the United States are afflicted with arthritis and rheumatism. Estimates of the cost to the nation from diabetes, anemia, and other metabolic diseases are unavailable. The total would easily equal that for arthritis.

It is estimated that of the 10 million Americans afflicted, more than 250,000 are completely disabled and 4,700,000 are disabled part of the time. Arthritis accounts for most of the complete disability. With the proper application of present knowledge, it would be possible to prevent the crippling in three-fourths of all cases. Unfortunately there is a great shortage of trained physicians and, as a result, the knowledge we have is not always properly applied. In addition, further research is necessary before it will be possible to treat successfully the remaining one-fourth of the victims of rheumatoid arthritis. At present the cause of arthritis is unknown and there is no cure.

Diseases of Metabolism

The best known of the diseases of metabolism are diabetes mellitus, which afflicts an estimated three million Americans, and obesity, which affects a quarter of the adult population. Obesity is not only disfiguring; it shortens life by predisposing to other

serious chronic diseases and by lowering the chances of survival in surgery and other major stress.

Also included among the prevalent diseases of metabolism are anemias of several types, the nutrition deficiency diseases, disorders of the hormonal system and diseases of the liver such as cirrhosis.

There are about 1,600,000 known diabetics in the United States and it is estimated that an additional 1,400,000 have the disease but are unaware of their condition. About 25,000 individuals die each year as a direct result of this disease and it is estimated that, on the average, diabetics are disabled 15% of the time. Diabetes cannot as yet be cured and comparatively little is known about its prevention. Failure to understand these and other diseases due to metabolic defects results from a lack of adequate knowledge of the fundamental processes of metabolism (processes by which food is assimilated and used for the necessary purposes including the building of bone and muscle during growth, the performance of work and the maintenance of all body functions.) Therefore, basic research in metabolism is stressed both in the Institute's direct operations and in its grants-in-aid program.

Organization

From the beginning, major emphasis has been placed upon research and training, and the Institute's activities in this area have grown

steadily and impressively during the past few years. The two major program areas of intramural and extramural activities are further conveniently divided into several areas to meet the problem of research and training.

Intramural Research

Approximately one-sixth of the money appropriated to the Institute each year goes to support direct operations, the so-called intramural research carried out at Bethesda, Maryland. In addition to basic laboratory research, NIAMD scientists also conduct clinical studies on a limited number of specially selected patients. It is the policy of NIH to admit to the Clinical Center only patients who are suitable for clinical research and who fulfill the requirements of specific research projects currently in progress.

Direct Activities

The Clinical Investigations program of the Institute is subdivided into such branches as Arthritis and Rheumatism, Clinical Endocrinology, Metabolic Diseases and Pediatric Metabolism. In intramural and collaborative research, among the basic laboratories and subsections, there are Laboratories of Nutrition and Endocrinology, Biochemistry and Metabolism, Experimental Pathology, Pharmacology and Toxicology, Chemistry, Physical Biology, Molecular Biology, Epidemiology and Biometry.

Extramural Activities

The extramural program accounts for approximately 85 percent of the Institute's yearly funds and is designed to support research and training in the Nation's medical schools, universities and other research centers. Extramural operations include a Research Grants Branch, Training Grants Branch, and an Operations Branch.

Money and Manpower

In 1963, the NIAMD employed 298 technicians, 135 professional Civil Service scientists, 31 visiting scientists from private research centers and universities, and 95 United States Public Health Service Commissioned Officers. In addition, more than 100 workers were employed for supporting functions to the scientific staff.

Budget summary (operating level - FY 1963)

Grants:	
Research	$70,822,000
Fellowships	3,927,000
Training	12,784,000
Total grants	87,533,000
Direct Operations:	
Research	10,690,000
Collaborative studies	900,000
Review and approval of grants	1,305,000
Program direction	370,000
Total, direct	13,265,000
Total obligations	100,798,000

Progress in Arthritis Research

The field of the rheumatic diseases during the past decade has undergone a tremendous change from what it was prior to the establishment of the Institute. The discovery of the remarkable anti-inflammatory effects of the steroid hormone cortisone in 1948 marked a striking advance. Prior to the advent of cortisone, the rheumatic disease field was one of the most neglected areas in medicine and little headway was being made in either understanding or treatment of such disorders as rheumatoid arthritis, osteoarthritis, gout, and other rheumatic diseases.

It was soon found, however, that along with beneficial effects cortisone also produced many undesirable, and sometimes dangerous, side effects. Thus began the search, which has continued ever since, for similar drugs with the same beneficial effects but fewer or no undesirable side effects. The hope that such drugs might be found or synthesized in the laboratory was partially realized in 1954 when Dr. Joseph J. Bunim, Clinical Director of the Institute, tested clinically the first effective anti-rheumatic synthetic corticosteroid drugs, prednisone and prednisolone. These drugs had been synthesized by the pharmaceutical industry and were given extensive clinical study at the Institute before being released. The search still goes on and newer drugs have been introduced, but none has so far proven superior in any significant way to the original prednisone and prednisolone.

Equally as important as the advances in treatment that have occurred during the past decade is the amassing of knowledge about the basic causes of rheumatoid arthritis and the exact mechanisms which lead to the disease processes. During the past five years Institute scientists and grantees have made major advances in the understanding of the so-called "rheumatoid factors" found in the blood of many patients with rheumatoid arthritis. Their work has shown that immunologic mechanisms are operating in the disease and play an important role in its development.

The experimental studies and speculations that center around the rheumatoid factors have led to a better understanding of many aspects of rheumatoid arthritis and have opened up new approaches to the broad field of immunopathology. In addition, rheumatoid factor studies have provided a useful tool in epidemiological and prospective studies of the rheumatic diseases which have hitherto been difficult or even impossible.

Progress in Metabolic Research

Metabolism is an almost boundless research area which is being intensively studied by Institute scientists and grantees. Some of the diseases in this area, like diabetes, are well known and frequent while others, such as alcaptonuria and phenylketonuria, are relatively rare.

Diabetes is a hereditary metabolic disease the main defect of which is the body's inability to metabolize carbohydrate normally.

As a result, the diabetic is unable to utilize efficiently the carbohydrates he consumes and to turn them either into heat and energy needed for normal body functioning or store them in the form of glucogen. Instead, the carbohydrates, converted into glucose, accumulate in blood and tissues and spill over into the urine. Primarily, this occurs because of a diminished supply or availability of insulin, a hormone produced by the pancreas, although many other factors are now known to be involved. Not only is there a decreased production of insulin but there may also be impairments in the way insulin acts. Also, major disturbances in the metabolism of fats and proteins accompany the defect in carbohydrate utilization. It is a complicated disease about which much more needs to be learned.

Ideally, the aims of treatment in diabetes are to facilitate normal carbohydrate metabolism, reduce the abnormally high levels of sugar that exist in blood and urine, prevent the occurrence of diabetic coma which can arise from too little insulin, maintain normal weight, and prevent the serious degenerative complications from developing in blood vessels and nerves.

Although the epoch-making discovery of insulin provided the diabetic with an effective means of controlling his disease, it also presented many new problems. Insulin can only be given by injection, a procedure which is painful and unpleasant to some, and distinct hardship to some others who must depend on someone else for injections. Additionally, the diabetic faces the hazard

of insulin shock and must adhere to a rigid schedule of eating and physical exercise. Because of these disadvantages, almost from the moment of insulin's discovery the long search began for a drug which, unlike insulin, could be taken by mouth to reduce the abnormally high level of blood sugar and help the body metabolize sugars and starches.

Within the past ten years, the search has been rewarded with several new drugs, the so-called oral hypoglycemic agents which can lower blood sugar levels without producing serious side effects. Three such drugs currently in use: tolbutamide ~~and~~ chlorpropamide, which belong to a class of compounds known as the sulfonylureas, and a third one of a different type, phenformin. These drugs are still far from an "oral insulin", but they are effective in an estimated one-third of the country's diabetics.

Prediabetes

In other clinical work in diabetes the emerging concept of "prediabetes" has been of importance. It has been expressed in the statement: "Before you are born, you are prenatal; before you are diabetic, you are prediabetic," and it refers to the belief that impaired carbohydrate metabolism as diagnosed by the standard glucose tolerance test for diabetes is actually one of the later changes to occur in the diabetic, not one of the first ones. From a genetic standpoint a person is probably prediabetic at birth,

though he may continue to have a normal glucose tolerance test for years.

Due to diligent search by imaginative investigators, it has now been established that other chemical and anatomical changes antedate abnormal blood glucose levels in many cases. If they can be detected prior to any observable disturbance in glucose metabolism, the prediabetic state may be a better time for instituting treatment in the hope of preventing progress to frank diabetes and the early appearance of degenerative anatomical complications of the disease. Several tests for these changes have been devised by one group of Institute grantees. The tests include photography of blood vessels in the eye, and electron microscopy of ear lobe biopsies; early results indicate that they may have vaule in detecting the "prediabetic." In service research efforts are directed presently toward elucidating additional useful diagnostic landmarks in the prediabetic state.

From the patient's point of view, the continuing advances being made in the treatment of diabetes constitute one of the brightest features of contemporary medicine. As a result of these developments, such as the discovery and widespread use of the new oral antidiabetic drugs, the outlook for persons with diabetes has improved materially in recent decades.

Cystic Fibrosis

Another disease of considerable interest is cystic fibrosis, a grave disease of children, adolescents and young adults. It is thought to be caused by an inborn error of metabolism, a basic defect which produces a widespread disturbance in certain exocrine glands, the sweat, tear and salivary glands, and many of the mucus producing glands of the body. It is a highly fatal disease in which chronic and progressive pulmonary disease is the most critical development. Since over 90 percent of the deaths occur because of the lung involvement, trials of newer antibiotics and bronchial mucus-dissolving agents are an important aspect of current research.

In NIAMD's Pediatric Metabolism Branch, attempts to discover the basic defect in cystic fibrosis involve both biochemical and immunological methods. Sensitive screening techniques are being used to locate any abnormal constituents common to all the organs and tissues of cystic fibrosis patients.

Gastroenterology

Among the medical specialties, gastroenterology has undergone one of the greatest relative changes within the past decade. It is a field of enormous scope, in terms of the number of people

affected by disease. Encompassing all the diseases of the digestive tract, gastroenterology includes such well known disorders as peptic ulcer, regional ileitis and ulcerative colitis. During the past ten years, newer techniques of studying digestive physiology, methods of obtaining biopsy specimens, and the use of isotopically-labeled materials have all helped to put research in this area on a sound, scientific footing.

Gastroenterological research is in a state of dynamic transition from the mild interest of a few years ago. A significant factor in this renaissance has been the granting of increased funds for research by the Institute and the effective manner in which they have been used.

Hematology

Hematological research is assuming an increasingly important role in the program activities of the Institute. Anemias of various types, and clotting disorders like hemophilia are but a few of the multitude of diseases known to affect the blood and blood forming elements. Considerable progress is being made at the Institute in discovering the basic mechanisms that are operating in some of these disorders. As in all scientific work, however, each new finding poses additional questions.

Extramural Research Program

The main objective of this program is to expand research in non-Federal institutions by awarding grants-in-aid to highly qualified investigators, for the support of promising research projects, careful selection being provided by the review mechanism of the program.

Each application is first analyzed by the Division of Research Grants of the National Institutes of Health and then assigned to an appropriate Study Section. These Study Sections are organized according to the various scientific disciplines and are composed of experts drawn from the faculties and staffs of leading institutions in the United States and Canada. The Study Sections carefully evaluate each application on the basis of competence of the principal investigator, merits of experimental design, significance of the project, adequacy of the available facilities and reasonableness of the proposed budget. On the basis of these considerations they recommend either approval or disapproval for the application. When an application is recommended for approval, a priority number based on its relative merit, is assigned to determine its competitive position for available funds.

The Advisory Councils

The application is then reviewed with equal care, but from a different viewpoint, by the Advisory Council. The Council, known fully as the National Advisory Arthritis and Metabolic

Diseases Council, takes into consideration matters of policy and program interest as well as the scientific merit of the proposal.

The Advisory Council is appointed by the Surgeon General of the Public Health Service and consists of four to six laymen who are leaders in education and public affairs, six to eight physicians who are eminent authorities in the categories of diseases represented by the Institute, and three physicians representing the medical departments of the Army, Navy and Veterans Administration. The recommendations made by the Advisory Council, which are based in part on the recommendations made by the Study Section, are then submitted to the Surgeon General of the Public Health Service for final action, and the applicant is advised accordingly.

The Extramural Training Program

Over the course of a number of years, many of the leaders in the rheumatic disease field, particularly those who were experienced in the area of medical education, commented upon the distinct need for a research training program in arthritis. At meetings of the American Rheumatism Association (ARA) and of the Arthritis and Rheumatism Foundation (A&RF) these needs were voiced and discussed. Members of the staff of the Institute and the Council also considered the problem and ways and means of solving it. The general consensus was that such a program, one which would provide funds for research and advanced clinical training in our medical schools or other research centers, was not only desirable but vital, for competently

trained manpower in the rheumatic disease field was the weakest link in the chain. The training grants program became a reality in 1955 and has since been extended to cover research trainees in dermatology, diabetes and metabolism, gastroenterology and nutrition, hematology and orthopedics. The training grants are awarded to institutions to initiate or improve current research training facilities in the rheumatic disease field. The funds may be used for a number of purposes: salaries for senior or junior staff members, stipends for qualified trainees, and for necessary ancillary personnel, for certain consumable supplies and permanent equipment; and for essential travel.

When applications for these grants are received, they are referred for initial review to the NIAMD Training Committee for the particular clinical specialty, and in the course of this consideration the committee visits the applicant institution to obtain first-hand information concerning the resources available and problems involved in setting up and administering the program. The problems, the needs and the possibilities are discussed with representatives of the institution concerned, and the committee obtains, as a result, a fairly good grasp of the situation existing at each institution visited.

The primary aim of the training grants program is to train for research and for academic careers in this area, to strenghten the research and teaching staffs in medical schools and research institutions by training new staff members.

The Institute also supports the training of investigators through its Fellowship program whereby qualified individuals receive stipends for training with highly capable sponsors but where the circumstances do not justify the establishment of a training grant activity. In this manner the Fellowship and Training Grant programs complement each other in a most effective fashion, making maximal use of available manpower and resources at minimal cost. Supported through the fellowship mechanism are the recent postdoctorals who require additional training of a specialized nature as well as the established investigator needing training in a new field or technique. The recently established Research Career Award program, which provides funds for the creation of additional stable research positions in qualified institutions, is also administered as a part of the Institute's Fellowship program.

The Epidemiology and Biometry Branch

The Epidemiology and Biometry Branch of the Institute is engaged in the application of medical and biochemical genetics along with other new epidemiologic and biometric methodologies to the investigation of arthritis and other metabolic diseases. It also plans and conducts field, ecologic and other appropriate studies in the U.S. and abroad for the purpose of understanding the causes or the nature of diseases of interest to the Institute where results are likely to advance the status of the health sciences in the United States.

International Nutrition Research

In addition to nutrition research carried out in its laboratories in Bethesda, the Institute supports the research components and research-related activities of the Interdepartmental Committee on Nutrition for National Defense (ICNND). During the past few years the international nutrition activities of the Committee have been accompanied by a measure of research work, much of which may be characterized as epidemiologic--the determination of facts concerning the incidence, distribution, and interrelationships of nutritional disease in different populations and geographic, climatic, and economic environments. This work has produced a variety of meaningful new information of considerable research interest in the United States. Thus, for instance, a study in South Vietnam of the relationships between goiter incidence, dietary iodine intake, and the ratio of iodine and creatinine in urine has contributed a new and apparently reliable index of dietary iodine intake.

In other studies evidence has been uncovered for a possible and hitherto unsuspected role of vitamin E in the formation of red blood cells, and additional knowledge has been obtained concerning the human requirements for a number of vitamins. This type of epidemiologic research has not only demonstrated a concrete relevance to domestic health problems and health needs, but has also been productive in revealing pertinent areas and new directions for the application of biomedical research.

Coordination with Allied Agencies

The Institute has developed close working relationships with two other allied organizations, the American Rheumatism Association, a professional medical group interested in the rheumatic diseases, and the Arthritis and Rheumatism Foundation, a non-profit fund-raising group. Close working relationships have been developed among the three organizations primarily concerned with the national attack on arthritis. Constant liaison and consultation on matters of policy, program, and operation is maintained. Constant contact is also maintained with other private or voluntary organizations, such as the American Diabetes Association, the National Hemophilia Foundation, and the National Cystic Fibrosis Research Foundation.

THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

The National Institute of Child Health and Human Development is the most recently established of the nine Institutes and four Divisions that make up the National Institutes of Health. Authorized by an act of the Congress in 1962, the Institute was officially established by the Surgeon General of the Public Health Service on January 30, 1963.

The Institute of Child Health and Human Development differs from the earlier established categorical Institutes in that it is non-categorical and its attention is not focused on any one disease or part of the body, but rather on the lifetime development of the whole person, with its complex health problems and requirements. The Institute seeks to provide emphasis, for example, on the special health status and particular needs of special segments of the population--such as infants, expectant mothers, adolescents, and aged persons--with common health problems which lend themselves to intensive study.

Specifically, the Institute will strive to develop more effective research efforts in such areas as the biological, physiological, and behavioral aspects of human reproduction, growth and development; studies of the prenatal and perinatal period in human development, from conception until shortly after birth; obstetrical and pediatric

problems not directly related to the specific disease interests of the categorical Institutes; studies on the process of maturation and senescence, including the biological, medical, and behavioral aspects of the aging process; and studies in special problem areas of human development, such as mental retardation.

The need for more extensive research relating to these problems is indicated by the fact that, in the last decade, the United States dropped from sixth to tenth place among the advanced nations in the saving of infant lives. Some 70,000 pregnancies result in stillbirths each year, and more than 110,000 American babies die before their first birthdays. Many of these early deaths are associated with defective development or premature birth. Mental retardation, congenital malformations, physical and psychological handicaps and other developmental defects of growth and behavior have emerged as significant problems to children, their parents, and society.

In addition, the processes of maturation and aging, which continue throughout the span of human life, are little understood and need much fuller investigation. Since 1900, the number of persons reaching the age of 65 has risen from 3 million to about 17 million. This is a jump of from 4 percent to over 9 percent of the total population. The medical, psychological, and physiological problems associated with aging have grown as the number of individuals in this older age group has increased.

Current Activities

Organizational planning and development of programs for the Institute have been its major responsibilities during the first months of its existence. The initial organization of the new Institute includes the staff and functions of the Centers for Aging Research and Research in Child Health, formerly located in the National Institute of General Medical Sciences. Additional program components of the new Institute will be established by transfer of a broad base of related research and training activities, giving these activities a more meaningful focus.

At present, the staff of the Institute consists of approximately 30 individuals--professionals and their supporting staff-who are primarily engaged in program planning and analysis activities. Funds for the initial operation of the Institute during the remainder of Fiscal Year 1963, totalling $448,000, were transferred from the National Institute of General Medical Sciences, and represent operating funds and salaries budgeted for the two special centers that were assimilated by the new Institute when it was established.

THE NATIONAL INSTITUTE OF DENTAL RESEARCH

Purpose and History

Diseases of the oral cavity and related structures constitute one of the major public health problems in the United States. While these problems can be partially alleviated by increasing the nation's resources of dental clinicians, the most promising approach is research activity directed towards increased knowledge of the causes and prevention of these diseases.

Public Law 755 (the Dental Research Act) formally established the National Institute of Dental Research in June 1948, providing a mandate for the conduct and support of research on the causes underlying oral diseases and related conditions. The Act had as its purpose "to improve the dental health of the people of the United States through the conduct of researches, investigations, experiments and studies relating to the cause, diagnosis, and treatment of dental diseases and conditions; assist and foster such researches and other activities by public and private agencies; provide training in matters relating to dental diseases and conditions; and promote the coordination of all such researches and activities and the useful application of their results, with a view to the development and use of the most effective methods of prevention, diagnosis, and treatment of dental diseases and conditions."

This same legislation authorized funds for the construction of appropriate laboratory facilities to accommodate the newly created Dental Institute. However, the funds--$2,000,000--were not appropriated at that time. During the ten years that followed, Congress, the U.S. Public Health Service, the American Dental Association, and the citizens of the United States, endorsed the continuing need for appropriate dental research facilities at the National Institutes of Health. During this same period, construction costs almost doubled and the price of the building which had been estimated in 1948 to be $2,000,000 had risen to $3,700,000 by 1958. An appropriation of $100,000 provided in 1948 for architectural drawings had to be doubled eight years later.

Finally, on August 1, 1958, President Eisenhower signed the appropriation bill for the Department of Health, Education, and Welfare, which included provisions for $3,700,000 to finance the construction of the long awaited research building to house the Dental Institute.

The Institute was installed in its research building at the National Institutes of Health in 1961 and its research to provide the newer knowledge and techniques to advance the practice of dentistry took a long step forward. The basic scientific data now being accumulated contribute to our resources in the fighting of oral diseases and also to the improvement of the general health of this nation and of other countries of the world.

The Institute of Dental Research provides a link between the scientist and the practicing dentist as well as a connecting force in the community of scientific investigators in universities and research institutions throughout this country and to some extent throughout the world.

Problems of Dental Research

Dental caries is the most prevalent of all diseases, affecting more than nine persons in ten. The staggering accumulation of untreated teeth far exceeds the capacity for corrective redress. It is estimated, for example, that there are almost one billion unfilled cavities among the nation's population. To provide necessary remedial care for these neglected teeth alone would require the equivalent of no less than 180,000 dentist-years at an approximate cost of three and one-half billion dollars.

Diseases of the supporting bone and gingival tissues affect at least half of the population by age fifty and almost all by age sixty-five. The magnitude of this problem is apparent from the fact that more than half of all dental extractions are the direct result of periodontal involvement. The cost to the American people attributable to this disease alone amounts to hundreds of millions of dollars annually.

Children born with crippling anomalies of the lips and palate are accumulating at the rate of approximately six thousand new cases per year. Only a fraction of these tragically afflicted children, who collectively comprise more than one-tenth of all those with major congenital defects, are receiving the optimum of skilled professional care required for their successful rehabilitation.

Surveys of children have shown that four out of five suffer from some form of malocclusion. It is estimated that two million children born each year will eventually require orthodontic care. However, with the present resource of trained orthodontists, less than one-fifth of these children could receive treatment. At this rate the disparity between needs and corrective capacity is apparent.

Estimates by industrial health specialists indicate that as many as 85 million man-hours of industrial production time are lost annually due to oral diseases. The progressive, cumulative nature of oral conditions means more treatment time, placing an enormous burden on a profession already critically short of manpower.

Although in the aggregate Americans pay about $2 billion yearly for dental care, this represents treatment and care for less than half of the people who need it.

While these dental conditions constitute major areas of research and educational responsibility, the scope of the activities supported intramurally and extramurally by the Dental Institute covers a much broader field. This includes oral manifestations of systemic disease, influences of oral disease on other organ systems of the body, oral cancer, surgery and prosthetic design for maxillo-facial rehabilitation, biological evaluation of newer technics of dental treatment, speech physiology and pathology, and genetic patterns and epidemiology of oral diseases.

Although a successful resolution of the many existing dental problems is dependent upon research, research itself is dependent upon the availability of trained scientists. It is for this reason that in the mandate to the

National Institute of Dental Research provision is made not only for the conduct and support of research but for the training of scientific manpower to conduct the research of the future.

Organization

The Institute's intramural research programs are conducted within an organizational structure of laboratories, branches and sections representing a wide range of disciplines and skills in the biological and medical sciences. An Extramural Programs Branch with subordinate sections on research grants and training programs administers the broad activities of awards for research, research training and fellowships.

To carry out its varied programs the Institute had on April 1, 1963, a total staff of 100 professional personnel (including visiting scientists) and 156 supporting personnel.

Operating relationships are maintained with all other Institutes, Divisions and Branches of the National Institutes of Health through formal meetings, seminars, and daily personal contacts. In addition, the Institute maintains close liaison with the dental activities of other areas of the Public Health Service, with universities and institutions engaged in dental research and training, and with public and private agencies in the field of dental practice, research, training and related activities.

The Office of the Institute Director is responsible for over-all planning, direction, and coordination of the Institute's programs. This office manages and administers the operating activities of the Institute.

The Laboratory of Microbiology studies bacteria, fungi, spirochetes, and viruses presumed or known to cause oral diseases; investigates the microbiology of dental caries and periodontal disease and of microbial metabolism in relation to the etiology of these diseases; investigates the relation of the oral flora to systemic diseases of man and to experimental dental caries and other infections induced by the oral flora in animals, especially in germfree animals; studies the effects of antibiotics on microorganisms related to dental diseases and conditions; and carries on fundamental investigations of factors regulating the ecology of the oral flora.

The Laboratory of Biochemistry conducts research on the biochemical aspects of oral diseases and the relation of dietary factors to dental caries etiology; studies the biosynthesis and chemistry of proteins in relation to metabolic function, collagen chemistry and enzymatic activity in inflammation; investigates factors affecting the calcification of bones and teeth, the biochemistry of fluorine in man, and the physicochemical properties of mineralized tissues.

The Laboratory of Histology and Pathology conducts basic investigations on the microscopic structure, physical properties and chemical composition of oral hard and soft tissues, employing biophysical and histochemical methods; studies the normal ultrastructure of fully developed teeth and bones as well as their formation and calcification by electron microscopy, electron diffraction and X-ray microradiography; develops new methods for the demonstration and investigation of enzymatic

activities and specific organic and inorganic entities in normal and diseased hard and soft tissues; and investigates the mechanisms by which chemical agents proposed for the control of dental caries, such as fluoride compounds, react with the outer enamel surface.

The Epidemiology and Biometry Branch employs epidemiological and biometric methods to secure and evaluate information on the characteristics of oral diseases in population groups to determine their cause and enhance the possibilities of developing methods of control. Certain of these studies are carried out in collaboration with other Divisions of the Service and with other federal and non-federal agencies.

The Oral Medicine and Surgery Branch conducts research in the field of growth and development of the osseous and muscular tissues of the oral region; evaluates treatment procedures for abnormalities of the face and jaws; carries on research in oral pathology, including evaluation of the metabolic processes influencing calculus formation, and morphologic changes in the supporting tissues of the teeth in periodontal disease; conducts studies in periodontal disease and dental anesthesia; and conducts investigations to correlate dental problems with other biomedical fields.

The Human Genetics Branch investigates congenital malformations, especially facial clefts; gene substitution diseases, with particular reference to those affecting structures and functions of the head and neck; therapeutic measures for dealing with the deleterious effects of genetic mutations; the relative contributions of gene and environment; chromosome abnormalities; diseases resulting from serological

incompatibility; genetic factors in caries and periodontal disease; and the development of mathematical models for the use of high speed computers in the application of genetic theory and methods.

Each of the laboratories of the Dental Institute contributes significantly to our knowledge of the many problems of oral health and disease. In these activities, our laboratories have provided a significant element of leadership to the total national dental research effort. This has encouraged research development in the universities and carries over into the sphere of dental education. As a result, our horizons today extend far beyond the walls of the Institute's laboratories and reach into the allied biomedical, physical and behavioral sciences.

The Extramural Programs Branch administers the dental research grants program in cooperation with the Division of Research Grants. This Branch makes field investigations of applications for research projects and evaluates operating projects and programs. It administers the research fellowship program designed to increase the dental research potential by awarding fellowships to the most promising scientists. It also administers the graduate training program to increase research manpower in dentistry.

Among the hundreds of different programs conducted in dental schools and other research institutions are: studies in the mechanism of root formation; effects of trace metals on tooth development; transplantation of teeth; mechanisms of oral sensation; growth of face and teeth; immunity

to tooth decay; lymphatic flow in head and neck; oral lesions; effects of antibiotics on disease; effects of aging on dental tissues; dynamics of speech articulation; rehabilitation techniques; surgical techniques; endocrine relationships to oral health and disease; salivary gland function; and many, many others.

Support for the Institute Programs

The total appropriation for the National Institute of Dental Research for the current fiscal year is $21,199,000. Of this sum about one-fifth is devoted to intramural research while the remaining four-fifths is distributed, under careful supervision, to universities and other institutions for the support of extramural research and training.

Expenditures in fiscal 1963

Intramural research budget	$3,005,000
Extramural - research grants ...	$8,566,000
Fellowships	$1,230,000
Training programs	$3,527,000

Research Programs

Fluoridation. Today, some 40 million Americans are protected against tooth decay by fluoridated water. This protection is based on research previously carried out by this Institute. The death in 1962 of Dr. H. Trendley Dean, who had pioneered in this research, marked, in a way, the end of the first era in our study of dental decay. Dr. Dean, the first Director of the National Institute of Dental Research, started work in the 1930's on the mottling of teeth in certain geographic areas. He learned that this disturbance in tooth formation was due to an excess of fluoride in the water used for drinking and cooking. However, he showed that this same fluoride, when present in small amounts (optimally one part per million) would protect teeth against decay without any accompanying mottling.

Following these early studies, advances have been made in methods of adding fluoride to the water where it is deficient and controlling it where it is excessive. Related studies are exploring the practicality of vehicles other than drinking water (i.e., dentifrices, tablets and various foods) for administering fluorides to populations where communal water supplies cannot be fluoridated.

The study of fluoridation in which the Dental Institute has participated is a long story, most of which is now fairly well known. However, it is of interest that final field examinations were made this year in a 17-year study of fluoridation of the community water supply in Grand Rapids, Michigan. This program, conducted in collaboration with the University

of Michigan and state and local health authorities, demonstrated that water fluoridation is practical and effective in caries control and that optimal doses of fluoride cause no mottling of dental enamel.

Calcification Research. Institute study of mineralized tissue, by means of electron microscopy and diffraction, contact and projection microradiography, and other physical methods, has led to a particularly important observation that animal bones with relatively high fluoride content tend toward crystal perfection, thereby increasing their physical and chemical stability. Since bones and teeth share some common properties, this finding may be important in showing the causes of tooth decay and explaining the inhibitory effects of fluoride. Thus, for the first time, direct evidence is available to show the manner in which fluoride may act upon biological mineral to make it more stable. We may not only know more about teeth through this research, but may have some leads to bone diseases as well.

Dental Decay. In some parts of the world, decay is not a problem and there is no apparent correlation with fluoride content in the drinking water. For example, in parts of Alaska, dental decay is almost unknown, whereas in Iceland it is rampant. In Ethiopia, dental caries is virtually absent, but in several nearby African countries, the population is almost toothless by middle age.

Current field studies by Dental Institute epidemiologists, in collaboration with the Interdepartmental Committee on Nutrition for National

Defense, are assessing the influence of nutrition on the prevalence of dental caries, as well as its relationship to periodontal disease. The findings in these studies are being analyzed by computer methods. Several reports have been made and several others are in press.

The computer has made it possible to correlate a great many factors--nutrition, age, schooling, type of domicile, occupation, geographic location, behavior patterns, etc.,--for large populations. The factors that play a part in diseases of the mouth and teeth should become apparent through such studies. In some populations dental decay was almost unknown a century ago, but is widespread today. This striking change in population susceptibility must be studied in the light of current events and circumstances.

An outstanding development of recent years was the demonstration by Institute scientists that tooth decay is a transmissible and infectious disease. In their studies of rats and hamsters over a period of multiple reproduction cycles, they have, through the use of germfree technics and other methods, shown conclusively that a specific strain of streptococcus is the cause of dental decay in the rat, and another strain causes decay in the hamster. The disease is passed from one animal to another, but when the streptococcus is not present, the teeth do not become decayed.

The principal investigators who were responsible for this major achievement were honored with the Albert Joachim international prize for dental research, an award made only once in five years.

These laboratory leads are being carried into clinical investigation through collaborative studies in hospitals.

Periodontal Disease

Parallel with the expected advances in the prevention and control of dental caries, there emerges the interesting speculation that as more teeth are saved from caries, more susceptible tissue sites may be preserved for attack by periodontal disease. Since formation of dental calculus in the gingival area is recognized as the most important immediate factor in periodontal disease, systematic studies of calculus deposition are given high priority. A significant recent finding is that various species of streptococci outnumber all other types of microorganisms at all stages of calculus formation. This is contrary to the long held view that filamentous forms predominate. A possibility exists that adequate measures can be found to prevent ectopic calcifications (tartar) by the elimination of suspected causative bacteria.

Dental Institute scientists are also studying relationships between specific microorganisms and certain types of periodontal disease. The complexity of this category of disease is a real problem and there is a distinct possibility that it may in fact represent several different disease entities. However, since one causative organism is now identifiable in hamsters, the eventual prospect for antibacterial measures of control is encouraging.

Genetics

Since the association of oral diseases with hereditary factors has long been recognized, the Dental Institute has given major attention to studies in human genetics.

These have been pursued in Institute laboratories, as well as in collaboration with other governmental agencies and universities. Included have been studies of chromosomal abnormalities, particularly in regard to oral and facial deformities (cleft palate, etc.), and other problems of growth and development such as mongolism. In Japanese populations where there have been large numbers of cousin marriages, the effects of inbreeding, particularly on stature, size and dental eruption, also are being studied. Parallel investigations have been pursued in selected populations along the eastern border of the United States to evaluate the relationships of genetic factors to cleft lip and palate, defective calcification, susceptibility to dental caries and periodontal disease. In the course of these studies, two new disease syndromes characterized by such conditions as defective speech and mucosal changes in the mouth and eyes have been identified and described.

In related laboratory studies, the prenatal effects of various drugs is being assessed in rats. Current emphasis is being placed on a better understanding of the interrelationships between environmental and genetic factors in the pathogenesis of cleft palate and other congenital malformations.

Connective Tissue Studies

Extensive studies in this area have concentrated on the chemical composition and reactive groups in normal and diseased connective tissues. The significance of a newly discovered connective tissue fiber has become clarified, and it is now thought that it belongs to the elastin family

of tissues, with predominant relationship to areas of stress such as periodontal structures, blood vessel walls, tendons and ligaments. A companion study, conducted in collaboration with the National Institute of Neurological Diseases and Blindness, has tested a similar stain on a series of biopsy specimens from patients with amyotrophic lateral sclerosis and found for the first time that a characteristic connective tissue disorder occurs in over 60 per cent of these cases.

Other studies have shown that degradation of connective tissue and bone may occur at sites distant from an inflammatory focus. This has provided another link in the understanding of the processes involved in periodontal disease.

The Section on Protein Chemistry of the Laboratory of Biochemistry has done extensive research on the structure and function of connective tissue proteins. Results of studies on the subunit structure of collagen from a number of vertebrate species and different tissues of the same species, show that there are differing degrees of intramolecular cross-linking which vary with the maturation process. That is, the cross-linking appears to proceed at different rates and to different extents in different tissues and animals.

The mechanisms by which collagen may function to initiate and control calcification is not known, but studies are going on to determine what happens to proteins which calcify in such areas as the aorta.

Clinical Investigations

In clinical studies, Dental Institute scientists have developed an accurate system of age determination by microscopic examination of teeth--something of particular importance to legal medicine, but also of some importance to the anthropologists and paleontologists who study the origin and development of man.

Also under investigation have been: (1) an evaluation of new anesthetic agents; (2) determination of the effects of high speed cutting instruments on the dental pulp; (3) problems of speech associated with oral-pharyngeal anomalies; (4) palatal growth and development in the congenitally cleft child; and (5) factors related to benign soft tissue lesions of the mouth. In the latter study, investigators have been exploring the causes and treatment of such oral ulcerations as herpes simplex (fever blisters) and aphthous stomatitis (canker sores). Some interesting findings thus far in the investigations are that a different strain of herpes virus may produce the disease in recurrent attacks in the same individual. There has also been identified a transitional form of bacteria as a possible cause of aphthous stomatitis.

Extramural Research

There are currently 455 research grants in operation in 138 research institutions situated in 36 states and 13 foreign countries.

During the year research sponsored by the grants program has been devoted to most of the major areas of interest to dentistry. Among these are: adhesive restorative materials, cleft palate and other facial congenital anomalies, periodontal disorders, calcification, caries, growth and development, and epidemiological studies of oral diseases. In addition to clinical investigations, efforts have continued in those other aspects of dental research such as basic science studies related to oral health, dental public health, and studies to improve dental materials.

All 49 dental schools in the United States have now participated in the research grant program, and approximately 75 percent of the funds allocated for research projects are devoted to research support at these institutions and closely related dental clinics. However, it is gratifying to note that the remaining 25 percent of grants dollars is supporting dental research in general hospital and biomedical facilities, and represents the establishment of new, broad, interdisciplinary program projects.

Although the number of grants is too large to categorize here, some particularly significant projects include:

1. Development of a technique for determining chemical elements in dental tissues by the use of monochromatic x-rays for microradiography. By using the technique of x-ray adsorption, chemical elements of dentine

and other tissues can be identified and the morphology of a substance outlined as indicated by the differences in density of the substance. It is expected that this type of examination can contribute much to the understanding of the processes of calcification and decalcification.

2. Development of dental adhesives. A number of promising compounds are reported which show potential as dental materials. This involves their use as temporary and permanent restoratives, and as cementing and pulp capping agents.

3. A genetic study on cariogenesis. Major genes have been identified which affect the formation of dentin and enamel, but these uncommon defects account for only a minority of patients with caries. The susceptibility or resistance of the majority of patients is also genetically regulated, probably by several genes.

4. An epidemiological study on fluorine, including a salt fluoridation study in four Colombian communities. In this investigation, the effectiveness of sodium and calcium fluoride as salt additives in caries prevention are being compared. This study has special significance because of the fact that 100 million people of the Americas use water supplies unsuitable for fluoridation.

5. Interdisciplinary programs on periodontal disease. Abnormalities of tooth contact have long been recognized as contributing to the breakdown of the periodontal tissues, but up to this time no comprehensive study of the subject has been undertaken to include the relationship

of the whole complex of jaw movement in relation to the forces and pressures bearing on individual teeth. Results of this investigation will probably be forthcoming in the course of next year.

6. Multidisciplinary cleft palate centers at several universities. Investigations of cleft palate and other congenital anomalies of the facial region have been greatly expanded in the last year through the establishment of large research programs encompassing a wide range of scientific disciplines. These programs are utilizing a team approach by the medical, dental, and social disciplines to augment our understanding of oral-facial anomalies and to provide a better basis for optimal rehabilitation. The principle specialities of participation are maxillofacial surgery, speech pathology, otolaryngology, prosthetic dentistry and orthodontia.

7. Another example of an area where significant progress is being made is the development of a material which will bond to tooth structure and thus provide for more permanent restoration. One such project started during the year involves the synthesis of organic polymers and the study of their adhesive properties. An advisory committee consisting of outstanding scientists, representing the fields of dental materials, polymer chemistry and physical chemistry, has been formed to provide specific guidance to the Institute in this area.

It is apparent from the programs described that dental research covers fundamental and applied knowledge regarding the structures with which we are dealing, and the diseases which can occur in these structures.

The origins of disease, the prevention of disease, the treatment of disease, and the rehabilitation of the patient are all involved.

The need for rapid acceleration of dental research activities and the critical shortage of adequate facilities and manpower in the dental health field require the development of a new and broader framework for meeting these problems. Plans now call for the creation in academic environments of approximately five dental research institutes. These institutes will be set up similar to the NIDR intramural research laboratories in Bethesda with permanent staffs of full-time investigators. They will provide both clinical and basic research as well as training related to clinical and laboratory disciplines.

Training

The sum of $3,527,000 has been appropriated for training grants from fiscal year 1963 funds. These funds support 55 training programs and 198 trainees at 44 institutions located in 22 States and the District of Columbia.

A future goal is to expand training in the basic sciences and place more emphasis on training toward the Ph.D. degree. This will include programs in metallurgy, colloid chemistry, crystallography, and genetics, all of which are areas where serious manpower shortages exist in dental research.

NIDR has formulated plans to initiate special clinical research training programs in a few schools in the near future. A small number of dental students would be carefully selected for specific clinical research training in addition to work in basic science.

Fellowships The research fellowship program is directed toward training qualified scholars for research and academic careers in health-related basic and clinical sciences of interest to dentistry. Support is provided to the individual with special emphasis being placed on training in basic science areas such as biochemistry, physiology, histology and genetics which are related to the study of periodontal disease, cleft palate and oral disorders.

A total of $636,952 was awarded for 87 regular fellowships at 41 institutions located in 24 states, the District of Columbia, and one foreign country.

It is hoped to recruit more scholars under this type of award for training toward the Ph.D. in basic science departments. Training would involve research projects related to dentistry, thereby creating a further interest in dental research.

Research Career Awards are available to institutions in the United States on behalf of qualified candidates to provide increased numbers of stable career opportunities for scientists of superior potential and capability in the sciences related to health. Awards are intended to provide individuals with some measure of assured support reasonably early in their careers.

A total of $208,363 was awarded during the year for 16 Research Career Development Awards. These are located in 16 institutions in 12 states. No Research Career Awards have been made by the Dental Institute.

The successful resolution of oral health problems will depend on a total attack through research upon the diseases which plague us. Encouraging progress is being made in our knowledge of the causes and treatment of these diseases. Future exploration will undoubtedly produce more of the answers which we need, not only to lengthen human life, but to make it better worth the living.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

History and Development

The creation of the National Institute of General Medical Sciences, which dates its existence as an Institute from January 30, 1963, gives to the National Institutes of Health a single, integrated organization devoted to the specific support of research and research training in the sciences basic to medicine and biology. Now within the NIH structure there is an Institute which provides through each of its programs a foundation of basic research support which the categorical Institutes may use as a base for their own programs of disease-oriented research. The scientific disciplines supported by NIGMS underlie all biomedical research, no matter to what degree it is specialized.

The concept of an Institute devoted to such fundamental studies is relatively new to the NIH. It is a direct outgrowth of increased understanding in the scientific community and by the Congress of the United States that the importance of basic research increases by something like geometrical progression as scientists and the techniques of science become more and more sophisticated.

The legal basis for NIGMS activities is Section 301 and related provisions of the Public Health Service Act, as amended (42 U.S.C. 241 et. al), and Public Law 87-838. The preceding organization from which the new Institute derives was the Division of General Medical Sciences, created in July of 1958. This Division provided within the existing

structure of NIH an organization geared for the support by grants-in-aid of a wide variety of activities to the end that fundamental research problems could be studied; that future scientists could be trained for laboratory research; and that financial assistance could be provided to scientists already at work in the broad multidisciplines basic to biomedical investigation.

Some segments of the program which were originally part of the Division have been transferred to other units. The Clinical Research Center Program has been incorporated into the new Division of Research Facilities and Resources. The Center for Aging Research is now a part of the new National Institute of Child Health and Human Development. Programs presently supported by NIGMS which bear direct relationship to the mission of the new Institute will be shifted there when program plans warrant such changes. These and other shifts in program leave NIGMS with a clear definition of responsibility--the support of fundamental biomedical research of the broadest multidisciplinary character.

Beginning in 1963 the Institute will have for the first time a Council devoted solely to a consideration of its own programs. The creation of the National Advisory General Medical Sciences Council will be doubly advantageous. The present National Advisory Health Council, which since 1958 has advised the Surgeon General on Institute programs, will be more free to concentrate on broad problems, which is its primary mission. A second gain, the acquisition of a new advisory body with intimate knowledge of specific areas of general medical science, cannot fail to add another precise dimension to the valuable expert advice available to the Surgeon General.

The Bases of the NIGMS Programs

The current programs of the Institute are concerned with the development of life at all levels, including cellular and subcellular. For example, scientists supported by NIGMS are studying growth of tissue and organs and their functioning. In some laboratories, the physical structure and function of the whole human is being studied. Others, using modern methods of behavioral sciences, are investigating the reasons why humans act and interact as they do.

The over-all program of NIGMS is designed for flexibility and scope, providing a unique resource capable of enriching all science by the strengthening of the broad, general research capabilities of the private medical and bioscientific institutions in this country. Studies in anatomy, biochemistry, biomathematics, biophysics, molecular and cellular biology, enzymology, genetics, microbiology, and pharmacology are all receiving support from the Institute. Certain multicategorical clinical sciences, such as surgery, orthopedics, dermatology, pathology and anesthesiology, are within the Institute's purview. Some of the new methods of science--uses of electronic computers to help solve biological problems--are also supported. These range from the analysis of electrocardiograms to the determination of molecular structure by the analysis of x-ray crystallographic studies.

Corollary to imaginative programs of research of all kinds within its mission is the urgent necessity to train scientists to prosecute future research programs. For the training of research scientists,

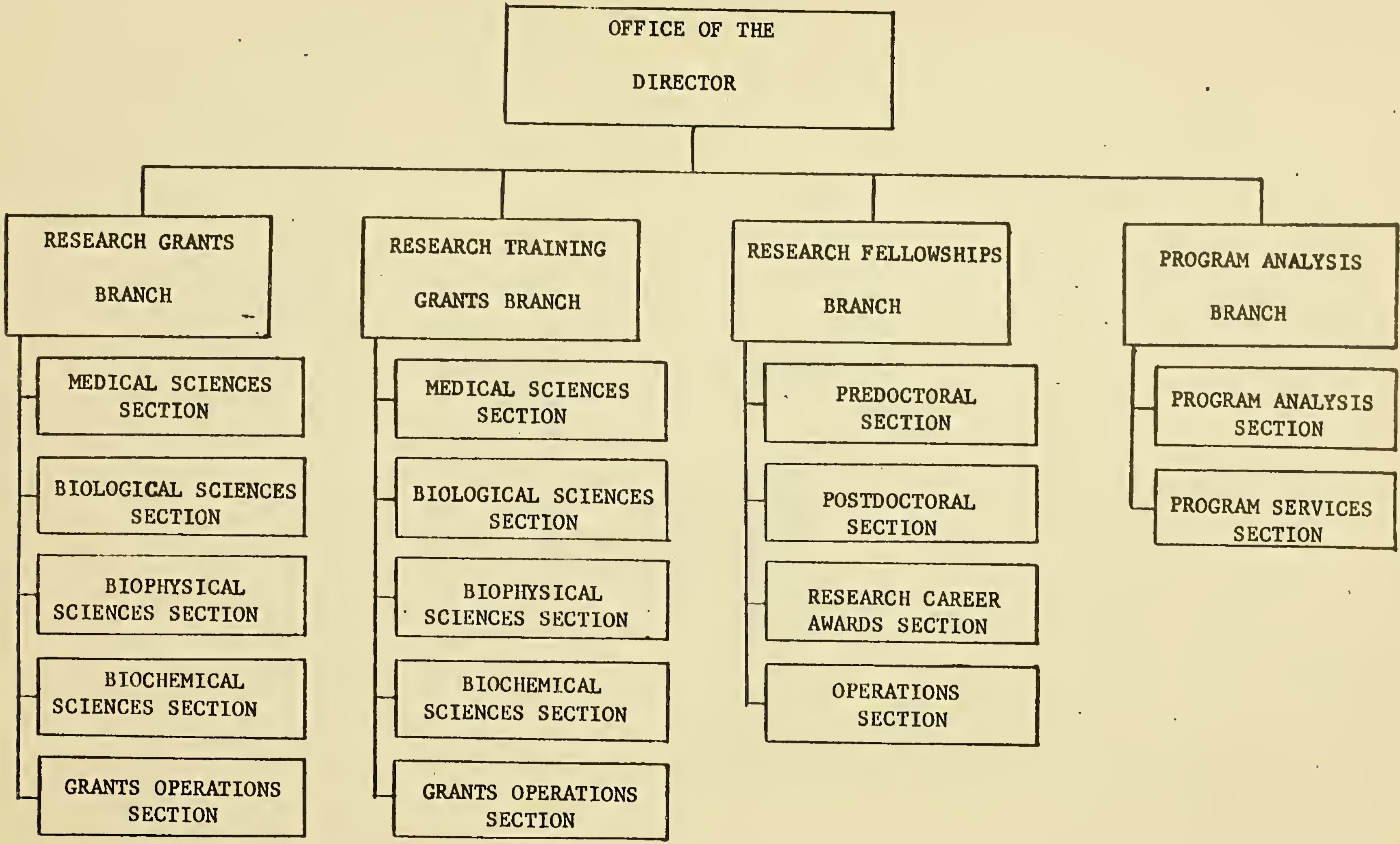
again in the basic biological and multicategorical medical sciences, the NIGMS has the second largest training grant program in any of the institutes at the NIH. Training is carried on in medical school departments and in hospitals with strong teaching staffs, as well as in selected universities which have high-calibre facilities for the training of potential scientists. Programs are now under way in many of the basic areas, i.e. anatomical sciences, biochemistry, biophysics, physiology, and pharmacology, to name only a few. Such education for research, conducted at the graduate and postgraduate levels, is extremely costly and often for this reason is beyond the financial capabilities of most universities, as well as often prohibitively expensive to the individual. There is in fact a consensus among well-informed scientists and scientific administrators that no university can afford to undertake this training without specific financial assistance of the kind provided by NIGMS. These are the programs from which will come the future researchers, some of whom will devote their skills to a continuing study of fundamental problems of human biomedicine. Others, building on the same fundamentals, will apply their knowledge to specific problems in health and disease. In whatever area they choose to work, ultimate benefit will accrue to the American people.

Each phase of the NIGMS programs, whether research grant, research training, or research fellowship, provides a sophisticated milieu through which the multiple goals of modern research can be more easily and expeditiously attained. Giving selected physicians greater-depth training in basic sciences, providing training situations in which medical students

can work with clinicians so trained, and in which medical and laboratory men can profit from cross-fertilization of ideas flowing from many kinds of research environments, these are examples of situations of obvious potential. Today's medical practice must rest on a firm scientific base. To reinforce this base, there is a growing imperative to make quickly and adequately available to the practicing physician the scientific fruits of the laboratory. No other NIH program is more specifically designed to provide the solid foundation of basic biomedical understanding from which can evolve more specific answers to the unsolved and urgent problems of modern medicine.

Organization and Budget

To accomplish its mission, the Institute operates three different programs through appropriate branches. These are the Research Grants Branch, the Research Training Grants Branch, and the Research Fellowships Branch. A fourth activity of the Institute is conducted by the Program Analysis Branch. An organizational chart, showing the internal structure of the Institute, and another breaking down the numbers of personnel, are given on the two following pages. The third chart included presents in simplified form the 1963 budget structure of the Institute.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NIGMS Personnel as of 12/31/62

Professional Staff		22
Ph.D.	16	
M.D.	4	
Dr.P.H.	1	
M.P.H.	1	
Supporting Staff		92
Total		114

Summary of 1963 Budget

The 1963 budget of the National Institute of General Medical Sciences is broken down into the broad categories listed below:

Research grants	$ 52,620,000
Fellowships	12,964,000
Training grants	33,676,000
Total grants	$ 99,260,000
Review and approval	1,450,000
Collaborative studies	583,000
Program direction	483,000
Administrative reserves, unobligated balances, transfers	7,670,000
	* $109,446,000

* Adjusted for recent shifts in programs.

Extramural Programs

The NIGMS program is wholly extramural. All of the investigations and the variety of training programs it supports are conducted in private institutions throughout the country and, to a limited extent, in foreign countries. These grant-supported studies will be described in detail.

Research Grants

On March 30, 1963, the Institute was supporting approximately 2,000 research grant projects in the basic biomedical sciences. These programs fall into four main areas: basic biological sciences, chemistry of life processes, clinical sciences, and development of new techniques and instrumentation.

It is acknowledged today that biology must concern itself not only with molecular relationships, but also with submolecular phenomena. It is more and more apparent that each part of a molecule of protein or of a nucleic acid has a specific significance in terms of specific activity and function. Working in this area, a grantee recently demonstrated that large molecules, such as proteins, can be sheared apart by ultrasonic action. In contrast to previously used chemical methods for fractionation, this procedure avoided alteration or denaturation of essential groups. As a consequence, more reliable determinations of the functions of the various parts of these large molecules are in prospect.

Studies in the basic biological sciences contribute directly and indirectly to the advancement of the medical sciences. Some of these areas now being investigated include studies on the physiology of the skin; regenerating systems and differentiation; effects of hormones on the development and aging of tissues; use of radioactive isotopes to determine the chemical basis of cell and tissue changes; preservation of tissues by freezing; mechanisms of protoplasmic movement; tissue cell growth, cell growth in culture media, cell division, and mechanism of incorporation of macromolecules into mammalian cells.

Aiming toward prevention and control of toxemia in humans, scientists are inducing this condition in lower animals so that the organs generally involved--the kidneys and liver--may be studied for characteristic changes.

With the ultimate aim of making it possible to graft skin and transfer intact organs from one human to another, studies are being made on animals of the same and diverse species. The immunologic processes which presently prevent grafting of tissues are fundamental, genetically related, and common to most animals. Within the past year there has been significant work in this field which points to the thymus gland as playing a role in transplantation immunity.

The thymus gland is the focus of interest of Dr. Albert Szent-Gyorgyi, Nobel prize winner and a long-term NIH grantee. After ten years of work, he and his associates succeeded in isolating two powerful

chemical substances from the thymus gland of calves. One of these is a potent promoter of growth, and the other an equally potent growth inhibitor. These properties were exhibited also in cases of experimental cancer in mice. Recent studies by these investigators suggest that the growth-stimulating factor "promine" actually consists of two substances, a growth-promoter and a juvenility or sterilizing fraction. These investigations have bearing both on cancer research and on the developmental sciences.

In the field of genetics, the Institute is supporting a considerable amount of work, including studies of the nature and distribution of gamma globulin factors which are expected to provide significant information about the ways in which persons differ chemically from each other, and about genetic control of protein synthesis in man. As the study of human chromosomes expands, various specific disease conditions and syndromes are being directly associated with irregularities in the chromosome set.

Research into various aspects of reproduction include spermatogenesis, ovulation,implantation and development of the embryo; and the structural, chemical, regulatory, and functional aspects of the processes by which a living organism begins with the fertilized egg. Studies attempting to delineate the causes of pathological conditions in the placenta are using the techniques of electron microscopy, immunology, histochemistry, pathology, and gross anatomy.

Investigations into the chemistry of life processes are concerned

primarily with three objectives: (1) the chemical constitution and the chemical nature of the metabolic products of living organisms, (2) the successive chemical steps by which living organisms carry on their metabolic processes, and (3) the mechanisms by which these processes are initiated and controlled.

During the past year the program in biophysics and biophysical chemistry has more than doubled, and the concepts and methods of the physical sciences and of the life sciences have been combined into a multidisciplinary approach to the problems of modern biology. The Institute supports studies on the mechanism of enzyme-substrate complex formation, investigations of the electronic interactions between nucleic acids and proteins, the configuration of biological macromolecules, the theory of polymers, and virus structure and function.

Studies of the synthesis of new organic compounds have led to the observation of the mechanism by which the absence of Vitamin E produces tissue degeneration in some animals, resulting in symptoms similar to those of muscular dystrophy in humans.

The first total synthesis of an antibiotic of the tetracycline group, an accomplishment which may lead to the development of greatly improved antibiotics, was achieved with the support of this Institute.

Another long-term grantee of the Institute, Dr. C. H. Li, recently won the Lasker Award for his work in isolating and identifying the adrenocorticotropic hormone (ACTH) and five other hormones of the anterior pituitary gland. He also synthesized a smaller molecule

containing about one-half the natural hormone's amino acids, and later synthesized a smaller fraction which promotes the breakdown of certain types of fat in the body. These studies have contributed greatly to the knowledge of metabolic disease, allergy, immunity, inflammatory disease, arthritis, and other diseases.

In the field of genetics, much attention is being focused on studies of the nucleic acids. So important is this area of investigation that a Nobel Prize was awarded during this past year to Dr. James Dewey Watson, an NIH grantee since 1957, for his work with Francis H. C. Crick in constructing a model of the helical shape of deoxyribonucleic acid (DNA). This molecule holds the key to the "genetic code" which furnishes instructions for the production of proteins and genetic material. The study of heredity, cancer, virus disease, mental disease, and a host of disorders designated as "inborn errors of metabolism" will be advanced by this fundamental achievement.

Other grantees are working on variations in the chemical organization of the nucleic acids, the nature of mutations, relations between DNA and RNA, the nature and function of the coding mechanism, and control of enzyme synthesis and protein specificity. Among the many approaches to these problems, computer methods are being applied to analysis of the collected data.

Some studies are aimed at determining the role of RNA (ribonucleic acid) in protein synthesis. RNA from different sources is being provided to growing cells and has been found to be accepted and to produce

proteins characteristic of the source. From this and other studies on the nucleic acids comes increased understanding of the genetic control of metabolic processes involved in the production of hormones concerned with such various processes as nerve transmission, excretion, differentiation, pigmentation, etc. It is from chemical studies that understanding of the function of an organism down to the molecular level is obtained. Biochemistry, biophysical chemistry and physiological chemistry all draw from each other to advance the general field.

Other grantees are studying the mechanism of ureteral peristalsis, and absorption of water and other substances through the skin. There is a continuing study of the sudden and unexpected death in children, and surgical studies are being continued on the replacement of limbs.

Knowledge of the chemical and physical forces and phenomena which influence biological activity is essential for the understanding of the pathogenesis of diseases, and there is new freedom in the use of information and techniques adapted from biology, immunology and physiology, as well as chemistry, physics and mathematics. In many university departments and hospitals, experimental work in pathology is combined with the physical and chemical approaches to the nature of normal and abnormal cellular functions ordinarily found in basic science departments. Consequently, new instruments are in use for studies of normal and pathological tissues and to aid in routine diagnoses and treatment of patients.

The electron microscope is used by grantees to study morbid histology, to observe change at the ultrastructural level of the cell,

and to correlate those changes with the chemical processes at the molecular levels that underlie function. Fluorescence microscopy is also widely employed in clinical research laboratories, as are the phase and interference microscope and the electrophoresis apparatus.

The great potentials of the computer as a valuable adjunct to biomedical research are being increasingly realized by the biomedical scientific community. Investigators are turning to biomathematics and bioengineering to aid in analyzing and bringing into logical sequence the data amassed in research. Investigators are exploring ways and means of using the computer as an adjunct to the physician in arriving at a medical diagnosis; others are concerned with the development of an automatic system for preparing lists of biochemical compounds which have been used for pharmacological tests and making this information available to investigators at frequent intervals after the results have been published. Other grantees are developing a data-processing computer that will perform a statistical analysis of biological responses while an experiment is still in process. Investigators have already developed a high speed analog-digital converter and an average response computer using magnetic drum storage. Support is also being given to the development of biomathematical techniques using the computer as a research tool. For example, computer programs are being developed which will describe the manner in which various body chemicals transfer from one compartment to another. The construction of these models will help to fill the gaps in our understanding of the vital body functions.

To further the development of this new hybrid science of bioengineering, the Institute supported a conference on amplification techniques in cell biology and has given support to the publication of papers presented at the Fifth International Congress of Electron Microscopists.

Training Grants

As the Nation's population increases and as our store of biomedical knowledge becomes more complex, we have ever greater need for a steadily increasing reservoir of high caliber, thoroughly trained scientists. Because it takes 10 to 15 years from the first year of college to prepare a scientist for a productive research career, training programs undertaken now must be tailored to meet the conditions which will exist in 1970 and beyond.

The research training programs of the Institute aim to attain these goals by (1) enhancing the potential of institutions to provide advanced training in the basic medical and health-related sciences through the support of research training staff and the supplying of modern research equipment, and (2) by stipend support to assist predoctoral and postdoctoral trainees toward research and academic careers. Emphasis is placed not only on the conventional disciplines but also on the interdisciplinary aspects of the biomedical sciences.

At the end of March, 1963, 662 biomedical research students were receiving support from the NIGMS Training Grants program. These

programs are described briefly:

The Graduate Research Training Programs supporting areas of recognized importance to basic biological research and research training such as behavioral sciences, biomedical engineering, biophysical sciences, and like areas. They are designed to help meet the Nation's increasing demands for trained scientific manpower in the shortage areas basic to medicine and health and thus meet the needs of medical schools and other research institutions for academic and research personnel in both present and future faculties.

The Medical Student Research Training Program, designed to serve as a screening and research orientation program for medical students by providing meaningful research training during summer, free quarter periods and drop-out years.

The Experimental Research Training Program, through which a limited number of projects for experimental research training at the undergraduate level have been recommended by the National Advisory Health Council.

The Medical Scientist Program, which will be started in 1963, aimed primarily at the provision of a graduate level of training in the basic and clinical sciences to prepare carefully selected students for research and academic careers in the clinical areas of medicine.

At present there are over 15 research training areas being supported by the Institute. These cover a broad range of the basic biomedical sciences and many are important to categorical research. The Institute

will also consider disciplines and subdisciplines that are clearly related to health and medicine, that are basic and non-categorical in nature, and that are highly in need of trained scientific manpower.

One area of strong interest, the Behavioral Sciences Training Program, supports trainees in the study of response-patterns of the intact organism in relation to the stimulus-characteristics of its environment. The basic disciplines in this area are generally recognized to be psychology, sociology, and anthropology.

Research training in the field of biomedical engineering is intended to meet the growing need for the application of engineering principles to biological problems. The major aim of the program is the design of research training embodying those engineering principles which are illustrated by servomechanisms, information theory, computer mechanisms, and devices for quantitation or utilization of biological data.

Training in the biophysical sciences leads to research in such currently active areas as radiation biology, physical properties of and interactions between macromolecules, theoretical biology, molecular biology, and mathematics of structure-function relationships and the application of new techniques of modern physics to problems in basic biology.

Anesthesiology is one area in which there is a critical shortage of trained professionals. The training program in this area has a

dual aim: to produce more trained anesthesiologists for research and for academic anesthesiology and to develop more training centers in this science. Programs initiated to date are beginning to turn out well-trained individuals who find appointments in medical schools and university hospitals.

To learn more about the causes of death from anesthesia, one project currently supported is an analysis of the amount and distribution of anesthetics in tissues. Another is concerned with systems of continuous monitoring of the physiological changes in patients under anesthesia. Answers to questions about the physiological reactions to anesthesia are being sought. Fundamental research is also under way to determine the molecular reactions by which so-called inert gases can produce the profound physiological changes associated with unconsciousness.

Research Fellowships

On March 30, 1963, the Institute was supporting 1,122 fellowships in three separate categories, Pre- and Postdoctoral and Special Fellowships.

The largest group, the Predoctoral Fellowships, are 897 in number. By its program of national competition, the Institute gives recognition to excellence of previous training and high potential for future development, offering an opportunity to learn more about the health-related sciences, particularly those areas in which the candidate is most interested.

Program areas receiving particular emphasis are biomedical engineering, biomathematics, and anatomical and physiological sciences.

The second largest group are the Postdoctoral Fellowships of which 260 were being supported in March 1963. These are awarded to promising holders of the following graduate degrees: Doctor of Philosophy, Doctor of Science, Doctor of Dental Surgery, Doctor of Medicine, Doctor of Osteopathy, and Doctor of Public Health. These fellowships are for advanced research training in the basic biomedical sciences and in certain special areas of recognized importance not receiving support from the categorical Institutes.

Awards in this group are available for three- to four-year periods with the intent of increasing the number of scientists qualified to carry out independent research. Currently, program emphasis is on the biophysical, developmental and behavioral sciences, and to the shortage areas of anesthesiology, medical genetics, biomedical engineering, biomathematics, physiology, molecular biology, and experimental pathology.

There were 65 Special Fellowships receiving support by NIGMS in March 1963. This is a group which provides an extremely high return on investment. Awards usually are made to scientists of some maturity with at least three years of postdoctoral training or experience and who require further specialized training or knowledge of new technics or disciplines in order to increase research productivity or to broaden their fields of scientific competence.

The inherent flexibility of this program has made it possible to support not only those contemplating additional training in traditional basic biomedical and health-related sciences, but in newly developing areas such as biomedical engineering, biophysical sciences, chemical genetics, molecular and radiation biology and radiochemistry, all of which have potential value to multicategorical investigations.

The Research Career program, established in 1962, supports 375 carefully selected individuals through Research Career and Research Career Development awards. The first provides support for established independent investigators of nationally recognized competence for the duration of their productive careers; the second for more limited periods supports investigators with demonstrated research potential who have not yet reached the stage in their scientific careers to qualify for Research Career Awards. Support is provided in a wide variety of health-related scientific disciplines, including anatomy, behavioral sciences, biochemistry, biomedical engineering, biometry, biophysical sciences, developmental biology, endocrinology, epidemiology, genetics, microbiology, nutrition, pathology, pharmacology, anesthesiology, physiology, as well as certain clinical research areas not readily identified with the interests of the categorical Institutes.

NATIONAL INSTITUTE OF MENTAL HEALTH

The National Institute of Mental Health -- authorized by the National Mental Health Act of 1946 as a result of growing public awareness of the need for more research, training, and services in the mental health field -- was established as one of the National Institutes of Health in 1949.

The NIMH, focal point for the Federal Government's programs in mental health, has three main purposes:

(1) Assisting in the development of State and community mental health services through grants-in-aid to the States, mental health project grants, and by providing consultation and technical assistance with respect to the prompt and effective application of new knowledge.

(2) Supporting and conducting research related to the causes, prevention, and treatment of mental illness and the improvement of mental health.

(3) Supporting the training of research personnel and of psychiatrists, psychologists, psychiatric social workers, psychiatric nurses, and other mental health workers essential to the provision of adequate services to the mentally ill.

The Background

The Federal Government's interest in mental health reaches at least as far back as 1928, when a bill was introduced into the Congress to authorize the construction of two hospitals for the confinement and treatment of persons addicted to the use of habit forming drugs. That bill was signed into law early in 1929.

The Act authorizing these two institutions created within the Office of the Surgeon General of the Public Health Service an administrative and investigative division then called the "Narcotics Division" which was charged with the administration of the two hospitals and with other responsibilities concerning narcotics, including research, information dissemination, and development of care and treatment facilities in cooperation with State and local jurisdictions.

The name of the division was changed to "Division of Mental Hygiene" by an Act of Congress approved June 14, 1930. All the authority, powers and functions exercised by the Narcotics Division were transferred to the new division. Scope of functions and activities of the newly created division were enlarged to include the making of studies and investigations related to the use of narcotic drugs and studies and investigations of the causes, prevalence, and means for the prevention and treatment of mental and nervous diseases.

World War II further brought into focus the mental health needs of the United States; during this time Selective Service had to reject some 900,000 men between the ages of 18 and 37 because of neuropsychiatric disorders, and by the discharge from the Armed Forces of an additional 700,000 men because of such disorders. This -- plus the efforts of dedicated professionals, educators, civic and religious leaders -- brought about passage of the National Mental Health Act of 1946.

The Act, P.L. 487 of the 79th Congress, provided for "improvement of the mental health of the people of the United States through the conducting of researches, investigations, experiments and demonstrations relating to the cause, diagnosis, and treatment of psychiatric disorders; assisting and fostering such research activities by public and private agencies, and promoting the coordination of all such researches and activities and the useful application of their results; training personnel in matters relating to mental health; and developing and assisting States in the use of the most effective methods of prevention, diagnosis and treatment of psychiatric disorders."

Establishment of the National Institute of Mental Health to administer this program was authorized by the Act.

With one exception -- the authorization of mental health project grants under Title V of the Health Amendments Act of 1956 -- the Public Health Service is operating its programs under authorities contained in the initial basic act of 1946.

Title V of the 84th Congress's P.L. 911 provided authority for mental health project grants to State mental hospitals and other organizations for "... investigations, experiments, demonstrations, studies, and research projects with respect to the development of improved methods of diagnosing mental illness, and of care, treatment, and rehabilitation of the mentally ill, including grants to State agencies responsible for the administration of State institutions for care and

treatment of mentally ill persons and for developing and establishing improved methods of operation and administration of such institutions."

Finally, under the area of legislative support for the Nation's mental health program, the Mental Health Study Act of 1955 provided the basis for the historic study conducted by the Joint Commission on Mental Illness and Health. The Final Report of the Joint Commission was transmitted to the Congress in the spring of 1961.

By direction of the President in December 1961, following transmittal of the Joint Commission Final Report, the Secretary of Health, Education, and Welfare, in consultation with the Secretary of Labor and the Administrator of Veterans Affairs, initiated a study to determine recommendations for a broadened national program in the field of mental health and illness. Their findings and recommendations were reported to the President in December 1962.

Based, in part, on the recommendations of the Joint Commission and, in part, on the recommendations of the interdepartmental study group, the President in a Special Message to Congress in February 1963 proposed "a national mental health program to assist in the inauguration of a wholly new emphasis and approach to care for the mentally ill. This approach relies primarily upon the new knowledge and new drugs acquired and developed in recent years which make it possible for most of the mentally ill to be successfully and quickly treated in their own communities and returned to a useful place in society."

The President's program consists essentially of these points:

1. The provision of Federal assistance through planning grants for the development of comprehensive mental health programs by the States.

2. The support of expanded research in order to "push back the frontiers of knowledge in basic and applied research into the mental processes, in therapy, and in other phases of research with a bearing upon mental illness."

3. The extension of efforts to increase the supply of and improve the utilization of trained manpower.

4. The provision of special grants for demonstration projects to assist State mental hospitals to improve the quality of care, and to provide inservice training for personnel manning these institutions. This will permit the hospitals to perform a valuable transitional role, through the strengthening of their therapeutic services, by becoming open institutions serving their local communities.

5. The development of comprehensive Community Mental Health Centers through the provision of Federal support on a sharing basis for construction and early-year operation (initial staffing).

All of these recommendations can be carried out within existing legislative authorities with the exception of the final proposal which is proposed for implementation under House Bill 3688.

Appropriations

The years since 1948 have seen a progressive assault mounted against mental illness through NIMH activities. Total appropriations from the Congress in 1948 amounted to $4,098,000, while the total appropriated in 1963 was $143,599,000.

Extent of the Problem

As the country prepares to move forward in the mental health effort sparked by the President's proposals to return the care of the mentally ill to the mainstream of American medicine, accurate estimates concerning the need for mental health services are needed.

Overall Estimates

However, unlike some of the more clear-cut disease categories, it is difficult to obtain an accurate assessment of the occurrence and distribution of the mental disorders, since these encompass illnesses which may range from extremely mild to extremely severe, and include a whole range of psychiatrically related problems such as alcoholism, mental retardation, drug addiction, juvenile delinquency, and others.

Estimates of the number of mentally ill persons in the general population vary. However, the basis for the most frequently cited estimate of the number of people sufficiently ill to be in need of psychiatric treatment at any one time is the 1957 Baltimore survey by the Commission on Chronic Illness. This survey uncovered a mental illness prevalence rate for the non-institutionalized population of about ten percent, exclusive of minor personality or behavior disorders.

A later study that has attracted a great deal of attention is the Midtown Manhattan study, an eight-year research project supported by the National Institute of Mental Health to measure the total prevalence of all degrees of mental disturbance, from mild to extreme, in an urban population. It revealed that of a random sample of adults between 20 and 59 years of age, 2.7 percent were considered incapacitated because of extreme mental disturbance, another 7.5 percent were considered to have severe disturbance, and another 13.2 percent to have marked symptoms; together these three categories, considered "impaired," constituted 23.4 percent of the total. Only 18.5 percent of the sample were classified as being without some degree of mental disturbance; the remaining persons were considered as having either mild symptoms (36.3 percent) or moderate (21.8 percent).

It was considered that the "impaired" group had definite need for psychiatric therapy. In terms of actual treatment, however, the need was not even close to being met. For example, in the "incapacitated" group (which had the most severe symptoms), 15 percent were receiving treatment in a hospital and 10 percent in a clinic, but the remaining 75 percent were getting no help at all.

Patients in Public Mental Hospitals

Many intensive studies of the rates of first admissions to mental hospitals have been made in the search for data concerning the occurrence of mental disorders; in fact, at one time the first admission rate was considered to be the best measure of these disorders. More

recently there has been recognition that not all persons with serious mental illness are admitted to hospitals. Some are cared for in clinics, nursing homes, prisons, or in the offices of psychiatrists in private practice. Nevertheless, the question of hospital population assumes special importance in the light of President Kennedy's statement that "If we launch a broad new mental health program now, it will be possible within a decade or two to reduce the number of patients now under custodial care (in mental hospitals) by 50 percent or more."

Examination of current mental hospitalization trends demonstrates the dimension of the task to be accomplished. In the 10-year period 1946-55, the year-end resident patient population of public mental hospitals increased at an average annual rate of 2.1 percent per year, and reached a high of 558,922 patients at the end of 1955. From that point on, the population decreased steadily by an average annual rate of 1.1 percent, to 515,948 at the end of 1962. This reduction occurred despite the fact that admissions were increasing steadily at an average rate of 7.4 percent per year during the same period of time. Thus the population decrease was achieved by a more rapid turnover of patients, rather than by a reduction in admissions.

Patients in Outpatient Psychiatric Clinics

In 1961 the 1,307 outpatient psychiatric clinics reporting to the National Institute of Mental Health (out of 1,589 such clinics in the country) reported that they had a total of 446,130 patients under care during the year. Slightly less than half this number of patients were under 18 years of age.

The average number of patients under care for the Nation as a whole was 285 per 100,000 population; however, there were marked differences among the States. The highest was New York, with 899 patients per 100,000 population; the District of Columbia was next with 873; but eight States reporting clinic statistics to NIMH showed rates under 100 per 100,000 population.

Other Areas of Need

Besides the community studies, and reports of hospital and clinic patients, other estimates of need are directly related to the programs of the NIMH. In particular, data is needed relating to social problems with a mental health component; for example, data relating to alcoholism, drug addiction, and the mental health needs of the aging.

The National Institute of Mental Health has been charged with the mission of improving the mental health of the people of the United States.

This mission includes not only efforts to insure the adequate treatment of mental disorder in whatever facility is most appropriate -- be it community mental health center, mental hospital, general hospital, clinic, psychiatrist's office, or other means. It also encompasses, as already noted, attention to the special problem areas of alcoholism, drug addiction, juvenile delinquency, mental retardation, and aging, which have a mental health component. Further than that, the National Institute of Mental Health sees as part of its area of concern those

aspects of social and cultural life that affect the mental health of the citizens -- urbanization and automation, to name just two. Its program includes the search for devices to protect and promote the mental health of the country within the limits of a rapidly changing society.

While much remains to be learned concerning the epidemiology of the mental disorders and related problems, enough evidence is available to furnish guidance to those responsible for planning mental health and related facilities and services as the Nation moves ahead with the implementation of President Kennedy's mental health proposals.

The Nation's Mental Health Needs

The National Institute of Mental Health and the State Mental Health Authorities, on the basis of studies of all the various types of need, are focusing their attention on three major areas.

Personnel

The first is the need for personnel. It is a well-documented fact that there is at present a drastic shortage of both professional and non-professional personnel to care for the mentally ill, and the development of the community mental health centers proposed by the President will increase demands for trained workers.

The number of professional persons with recognized graduate training in the fields of psychiatry, clinical psychology, psychiatric nursing, and psychiatric social work increased from approximately

12,000 in 1950 to 29,500 in 1961. In his Message on mental illness and mental retardation, the President called for an almost twofold increase of all professional workers in the mental health field from about 45,000 in 1960 to approximately 85,000 by 1970.

Research

The second major area demanding attention is research. The President, in recommending an expansion of clinical, laboratory and field research in mental illness and mental health, noted that there is still much more we need to know. He declared: "We must not relax our effort to push back the frontiers of knowledge in basic and applied research into the mental processes, in therapy, and in other phases of research with a bearing upon mental illness. More needs to be done also to translate research findings into improved practices." One of the types of research which is attracting special attention is research designed to try out and evaluate the effectiveness of community-based mental health programs. The Institute is also placing major emphasis on research designed to find ways of preventing the occurrence of the mental disorders, and of minimizing the disabilities accompanying the mental disorders when they do occur. Through its training program, in an effort to encourage research, the Institute provides awards to promising young scientists and experienced investigators to enable them to pursue research activities.

Clinical Facilities and Services

The third major area is the improvement of clinical facilities and services within the community. As already noted, there were a little more than 1,500 psychiatric clinics in the country in 1961. This number falls far short of filling the need and, as in the case with all other health facilities in the Nation, some geographical areas are much better served than others. The expansion and improvement of other clinical services is also needed: psychiatric services in general hospitals, specialized mental institutions, both public and private; the therapeutic skills provided by psychiatrists practicing in the community and by other physicians.

To be fully effective, all agencies and individuals concerned with prevention, diagnosis, treatment and rehabilitation must work closely together. The President's mental health program, with community-based services as its keystone, is a means of assuring this kind of coordination. The Community Mental Health Center, as envisaged in the President's program, would be far more broadly based than either the traditional outpatient psychiatric clinic or the usual mental institution, and would be the pivot for future mental health activities within the community. The Center would be close to the patient's home and would provide preventive and diagnostic services, outpatient and inpatient treatment, and transitional and rehabilitation services. Basically, he would be able to proceed from diagnosis through treatment and recovery to rehabilitation.

The Scope and Organization of the NIMH

Since the establishment of the National Institute of Mental Health, there has been a basic change in the character of the national efforts in the field of mental health. Institute programs have evolved from a simple dimension of program effort oriented toward a beginning program of psychiatric research and mental health training to a complex, diversified system of Federal support of mental health activities on a broad national base. Program developments over the years have drawn a complex family of diverse scientific and professional disciplines into the mental health field, and there has been a marked intensification of mental health activities.

This has resulted in the emergence of improved techniques for dealing with the mental disorders, with large scale collaborative efforts, both in research and in the application of research knowledge; and a marked acceleration of program effort along specific disease or problem-oriented lines in response to public need as reflected mandates -- for example, alcoholism, drug addiction, psychopharmacology, juvenile delinquency, and mental retardation.

Against this backdrop of program growth and development, the NIMH has evolved a program structure that embraces substantially all aspects of mental health activity, from basic research to disease control and community programs. These programs have been administered as a unified whole which has maximum effectiveness in terms of an integrated, coordinated total mental health effort.

The Institute is organized around three major groupings: Intramural Research, Extramural Programs, and Program Development.

Intramural Research

The Intramural Research program of the National Institute of Mental Health is the world's largest single laboratory and clinical research organization in the field of mental health. It conducts hundreds of interdisciplinary studies each year. These studies range from the pharmacology and physiology of drug addiction, through biological and psychological factors in schizophrenia, efforts of stress on the human to the basic metabolic processes involved in mental retardation.

Extramural Programs

The Extramural Programs area of the Institute is charged with the responsibility for the development and administration of the Institute's support programs of research, training, and technical assistance. Further, it is responsible for the Mental Health Career Development Program, and the activities of the National Clearinghouse for Mental Health Information.

NIMH Staffs in the DHEW Regional Offices

Unique among the Institutes of the NIH, the NIMH has staffs in each of the DHEW Regional Offices. The professional staffs, representing the disciplines of psychiatry, psychology, social work and nursing, carry out the Institute's program of technical assistance

to the States. This responsibility, an extension of the PHS responsibility in the field of health generally, is viewed as a highly important one. Further, as a result of the close contact these staffs have with State program personnel, it is possible for the NIMH to develop programs which are responsive to the needs of the States and the people residing in those States. Examples of this are the programs proposed in the 1964 budget for inservice training, and demonstrations of better methods of care for the mentally ill.

Research Grants and Fellowships Branch

This branch is charged with the responsibility for the development and support of grant and contract programs in the area of mental health.

The programs supported through the Research Grants and Fellowships Branch constitute the foundation of research into mental illness and health in this country.

Training Branch

The Training Branch is charged with the responsibility for developing and administering the largest single Federal training program. Through grants, the branch supports training in psychiatry, psychology, social work, nursing, and the Biological and Social Sciences.

Whereas, the other Institutes confine their training activities to the provision of training for research workers the National Institute of Mental Health has been and is primarily concerned with the provision of training for service personnel.

Research Utilization Branch

The Research Utilization Branch serves as the catalytic force uniting findings from the research laboratory and field demonstrations on the one hand, and the agencies and groups responsible for developing mental health service programs on the other. Thus the functions of the Branch are threefold: (1) Assisting in the rapid development of integrated, comprehensive State and local mental health programs, (2) Translating research findings into operating programs; and (3) finding new ways of providing services and/or new methods for meeting community mental health needs.

The branch staff consists of a core of specialists in various substantive mental health areas who have had practical experience in mental health and public health programs and who are highly skilled in techniques for program development.

Mental Health Career Development Program

Like all Government agencies which must depend upon highly trained technical personnel to carry out their programs, the Public Health Service has faced a continuing manpower shortage. As a result of a task force recommendation made to him, the Surgeon General, in 1961, authorized the establishment of the Mental Health Career Development Section. The aim of this program is to provide the Public Health Service with the psychiatric manpower it requires to carry out its responsibilities in the mental health field. In 1963 there are 47 young physicians in training.

National Clearinghouse for Mental Health Information

The National Clearinghouse for Mental Health Information was established in October 1962. Establishment of the Clearinghouse was the direct result of a long-felt and often expressed need for a centralized source of information on all aspects of mental illness and health of such groups as the Council of State Governments, the National Association for Mental Health, and professional bodies.

Program Development

The Program Development area of the Institute is charged with the responsibility for the development and administration of its long-range program planning activities, its statistical and information programs, and for the conduct of field studies.

The Biometrics Branch

The Biometrics Branch is charged with (a) collecting, processing, and analyzing data on the extent of the problem of mental disorders particularly with regard to patients under treatment in mental hospitals and outpatient psychiatric linics, in general hospitals with psychiatric services, and in public and private institutions for the mentally retarded; (b) providing consultative services to State research bureaus on the organization of statistical services and on the design of followup, evaluative and other special studies; (c) providing consultative services on design of experiments, analysis of experimental data and development of mathematical models to the other branches and laboratories of the Institute, particularly to personnel engaged in basic and clinical research.

Professional Services Branch

The Professional Services Branch advises the Director in planning, developing, and coordinating the Service-wide mental health program. Further, it develops program proposals in new areas of program activity, and supports research projects in these areas to meet program development needs.

Mental Health Study Center

The Mental Health Study Center operates a community-based mental health facility in Prince George's County, Maryland, for research on community mental health. It develops multiple approaches to collect data on, and to identify, the social structure of a community population. In addition, and as a base to its research activities, it operates a demonstration mental health clinic providing direct treatment to families and consultation to community agencies.

Publications and Reports Section

With the goal of promoting public understanding of the nature of mental illness and its related public health problems, the Publications and Reports Section disseminates information about the various programs and activities of the NIMH. All media communication are employed, and the Institute maintains liaison with State agencies, schools, professional organizations, voluntary health, civic and service organizations, and mass media in order to advance public knowledge and understanding of mental illnesses.

Present Programs and Past Accomplishments

Intramural Research

Within its own laboratories and clinical facilities, the National Institute of Mental Health carries on an extensive program of clinical investigations and of laboratory research designed to expand fundamental knowledge of the nervous system and of human behavior. The principal facilities used for these purposes are: (1) the Clinical Center, the 500-bed research facility which houses the clinical research programs of the NIMH and the other Institutes, and which contains about 75 beds for psychiatric patients; (2) the William A. White Pavilion, a 225-bed facility at Saint Elizabeths Hospital in Washington, D.C., which houses the Clinical Neuropharmacology Research Center operated as a joint program by the Institute and the Hospital; and (3) the Addiction Research Center, a field station of the NIMH located at the Public Health Service Hospital in Lexington, Kentucky, the site of clinical and laboratory studies of drugs and drug addiction. In addition to these clinical and laboratory facilities, the Mental Health Study Center in Prince Georges County, Maryland, is a community unit whose general purpose and function is to provide a setting for the study of important mental health problems in a community.

The intramural program includes investigations of the causes, prevention and treatment of drug addiction; studies of aging, biological factors in schizophrenia, and chemical organization and

metabolism of the nervous system; and research on the initial stages of family formation with particular emphasis on the influence of the family of the growing child. In addition, there are investigations of the effects of family relations on all types of psychiatric illnesses, neuropharmacological and sociopsychological studies, and studies of stress and its significance to the human organism. In 1962, the NIMH intramural research activities totaled $9,180,000.

Extramural Programs

Over the years, the major program effort of the Institute has been accomplished through grants and related contracts. In 1962, for example, 85% of the total appropriation was for the support, through grants, of research, training, and community and technical assistance activities in non-Federal settings -- universities, research and training institutions, State and local mental health institutions and agencies.

Research

From its inception in 1948 until the end of fiscal year 1962, the National Institute of Mental Health supported over 2,900 distinct research projects through its program of research grants. These projects -- ranging in duration from one year to fourteen -- account for nearly 6,200 annual grants and a total of nearly $122 million in awards. This history of the Institute has been marked by a steady growth and diversification of research effort -- reaching a level in fiscal year 1962 of 1,343 grants and $30,158,896 in awards for studies

in a variety of specific problem areas. The growth of the NIMH research program has been accompanied by the initiation of a number of administratively distinct grant programs to meet special needs in the mental health field.

Among the major substantive concerns of the Institute have been the areas of mental retardation, child health and development, juvenile delinquency, schizophrenia, alcoholism, aging, drug addiction, and psychopharmacology.

In the area of mental retardation, the total expenditure of research funds between 1948 and 1962 was nearly $8 million; the level of support in 1962 was over $2 million. Among the major areas included here are studies of etiology of mental retardation; the diagnosis and treatment of the retarded; the psychological and social adjustment of the retarded and their families; and the care, management and training of the retarded.

Effort in the area of schizophrenia has also been heavy. From the inception of the NIMH research grant program in 1948 until the end of fiscal year 1962, 1,209 awards totaling $32,047,114 were made for projects in the area of schizophrenia; this represents roughly one-fourth of the total research grant effort to date. In 1962, over 220 projects, totaling nearly $8 million, were devoted to studies of schizophrenia. Here, too, the emphasis of the research varies over a broad area -- including, for example, studies of brain and body biochemistry; social and cultural factors; epidemiological studies; and analyses of treatment methods.

Research on psychopharmacological treatment of mental illness has grown from a very small proportion of the program to approximately one-quarter of the grant program in the past few years. From 1948 until the end of fiscal year 1962, 1,223 awards totaling $29,590,866 were made for research on the use of drugs for the treatment of mental illness. In 1962, 281 grants totaling $7,798,112 were awarded for this area of research.

NIMH has responded to the increased public interest and concern about the problem of juvenile delinquency by increased research grant support through the years. A total of 105 research grants has been awarded for the total sum of $6,108,822 between 1948 and 1962. In fiscal year 1962, 26 grants totaling $1,054,044 were awarded for juvenile delinquency studies.

Other special program areas which NIMH has supported include problems of the aging, alcoholism and drug addiction. Two hundred twenty-seven grants totaling $6,546,235 were awarded for studies of aging from the years 1948 through 1962. In 1962, 37 grants totaling $1,357,467 were devoted to studies of aging. Between 1948 and 1962, 202 grants totaling $5,186,412 were awarded for studies of alcoholism, while in 1962, 43 grants totaling $1,627,053 were devoted to this psychiatric and social problem. One hundred thirty-seven research grants totaling $2,710,982 have been awarded for studies of drug addiction between the years 1948 and 1962. In fiscal year 1962, 23 grants totaling $641,414 were supported for studies of drug addiction.

An important segment of the total research program has been devoted to basic research in the behavioral sciences. As part of this effort, scientists in the biological, psychological, and social sciences are being supported in their attempts to identify baseline data regarding human behavior. Such data are of considerable importance in the planning, execution and interpretation of clinical studies in mental health and illness.

All of the research described above has been supported through the NIMH extramural research programs other than the Title V program (which authorized the Mental Health Project Grants).

Training

Since 1948, the Institute has directed a major proportion of its total effort to the problem of mental health manpower. At first, the main concern was with the major professional mental health fields -- psychiatry, clinical psychology, psychiatric nursing, and psychiatric social work. The Institute supports graduate training in all these areas and has continued to invest a major share of its training efforts in the production of such personnel.

A second concern has been the problem of mental health research manpower -- to add to the scientific manpower pool and to seek some of the answers to the cause, etiology, and ultimately the prevention of mental illness. To accomplish this, the Institute supports programs for research training in psychiatry, psychology, social work and nursing, as well as programs in the biological and social sciences of relevance to mental health.

At present, as mental health needs continue to grow and as efforts to improve mental health become more extensive, a wide variety and increasing number of various kinds of personnel have become important to further progress -- occupational and recreational therapists, the legal profession, the clergy, and the psychiatric aide and mental health attendant. The seriousness and extent of the mental health problem is such that the broadest possible spectrum of manpower must be utilized.

The growth of the training program is shown by the growth of numbers and amounts of training grants awarded. Total amount awarded in 1948 for 62 grants was $1,140,079; awards in 1962 totaled $39,374,975 for 1,145 grants. Over that period, the Institute supported almost 1,500 training projects, at a total cost of approximately $185,000,000.

Awards have been made to training centers of all kinds, although more than 80 percent has been awarded to colleges and universities -- approximately one-half of which has gone to medical schools.

Numbers of trainees supported have also grown impressively. In 1948 a total of 219 graduate trainees received stipends. In 1962 this total had risen to 4,570 -- including 1,152 stipends for residency training in psychiatry, plus an additional 373 stipends in the special general practitioners' program. Also included were 976 stipends in psychology, 1,143 in social work, and 451 in nursing. Almost 500 additional stipends were awarded in such areas as research training in the biological and social sciences, pilot projects, and schools of public health.

There were 494 research fellowship awards in 1962, as compared with 19 in 1948, first year of the fellowship program.

In toto, the number of persons with recognized graduate training in the four core mental health professions increased almost two and one-half times between 1950 and 1960, while the grant total in all health professions increased about 30 percent over the same period of time.

Community Mental Health Services

A. Technical Assistance

A staff of expert consultants work actively with the representatives of public and private mental health organizations to communicate research findings and to advise and assist in their prompt and effective application in the treatment of mental illness nationally. Collectively these consultants serve as a bridge between the research laboratories and the mental health practitioners -- those who work directly with mental patients and those who are engaged in the administration of clinics, mental hospitals, general hospitals, day centers, and the host of community facilities with a concern for the care of the mentally ill.

This work began in 1948. A total of $381,000 was allotted to support these activities in fiscal year 1950. The fiscal year 1962 budget was $1,336,000.

Several special techniques were developed to disseminate new information in regard to the conduct of mental health services and to demonstrate the application of clinical techniques developed from research

findings. Demonstrations are primarily implemented in areas where the needs for new and improved treatment procedures have not been met. In fiscal year 1958, $65,000 was allotted for these demonstrations. The amount allotted for this activity in fiscal year 1962 is $319,000. During the intervening period twelve demonstrations have been conducted or are in progress.

Intensive workshops called technical assistance projects were started in 1955 to disseminate new information to State mental health representatives on the application of modern principles and methods to administer mental health services programs. These technical assistance projects are planned with representatives of the State Mental Health Authorities and are financed by the National Institute of Mental Health. Since 1955 a total of 135 technical assistance projects have been held in 46 States at a cost of $540,000. Thirty-three technical assistance projects were held in 1962.

B. Grants to States

The National Institute of Mental Health has administered the mental health grant-in-aid to States since 1948. This program is administered under authority of Sec. 314(c) of the Public Health Service Act. Grants which States must match dollar for dollar are made to the agency in each State designated as the "Mental Health Authority." Funds are made available to assist States in prevention and control of mental illness through establishing, maintaining, and expanding community mental health services.

In fiscal year 1948 a minimum grant of $20,000 was made to each State with the States expending an aggregate of $1,653,454 of grant-in-aid funds. The State Community Mental Health Programs expanded and additional funds were appropriated to stimulate further activity on the part of the States in community mental health. The minimum grant to each State in fiscal year 1955 was reduced slightly to $17,750 but the total amount expended by States increased to $2,339,627. Further increases in grant appropriations enabled the minimum grant to be raised to $65,000 in fiscal year 1962 and the total of grant funds expended by the States reached $6,633,839.

The States primarily utilize the grant funds to develop and assist in the operation of mental health services including clinics. Because State and local expenditures for community mental health programs have been expanding a great deal more rapidly than has the amount of grant-in-aid funds appropriated, the Federal portion of total funds budgeted for these services decreased from 27 percent to 7 percent in 10 years.

C. Mental Health Project Grants

From its inception in 1958 until the end of fiscal year 1962, the NIMH supported 400 distinct projects through its program of Mental Health Project Grants. These projects -- ranging in duration from one year to seven -- account for over 400 annual grants and a total of over $25 million in awards. The history of this program has been marked by a steady growth and diversification of effort -- reaching a

level in fiscal year 1962 of 248 grants and $10,108,959 in awards for studies in a variety of specific problem areas.

Among the major substantive concerns of the Institute have been the areas of mental retardation, child health and development, juvenile delinquency, schizophrenia, alcoholism, aging, drug addiction, and psychopharmacology.

In the area of mental retardation, the total expenditure of Mental Health Project Grant funds between 1958 and 1962 was nearly $5 million; the level of support in 1962 was over $2 million. Among the major areas included here are studies of the diagnosis and treatment of the retarded; the psychological and social adjustment of the retarded and their families; and the care, management and training of the retarded.

Effort in the area of schizophrenia has also been heavy. From the inception of the NIMH Mental Health Project Grant Program in 1958 until the end of fiscal year 1962, 263 awards totaling $8,786,485 were made for projects in the area of schizophrenia. In 1962, over 50 projects, totaling nearly $2 million, were devoted to studies of schizophrenia. Here, too, the emphasis of the program ranges over a broad area -- including, for example, social and cultural factors; epidemiological studies; and analyses of treatment methods.

NIMH has responded to the increased public interest and concern about the problem of juvenile delinquency by increased Mental Health Project Grant support through the years. A total of 241 research

grants has been awarded for the total sum of $5,766,610 between 1958 and 1962. In fiscal year 1962, 45 grants totaling $3,358,178 were awarded for juvenile delinquency studies.

Other special program areas which NIMH has supported include problems of the aging, alcoholism and drug addiction. Twenty-six grants totaling $652,886 were awarded for studies of aging from the years 1957 through 1962. In 1962, six grants totaling $227,338 were devoted to studies of aging. Between 1957 and 1962, 30 grants totaling $1,100,311 were awarded for studies of alcoholism, while in 1962, 15 grants totaling $530,350 were devoted to this psychiatric and social problem. In fiscal year 1962, six grants totaling $191,383 were supported for studies in drug addiction.

Program Development

The Institute carries on continuous program development activities in areas of significance for the entire field of mental health. Work in a particular problem area, performed in part through special program activities of the Professional Services Branch, begins by a survey and evaluation of current knowledge and activities in the field. The relevance of mental health concepts and the techniques applicable to the particular problem are carefully considered and, as program solutions are developed, they are integrated into the Institute's operating programs -- training, research, and community services.

Some of the areas which are currently receiving consideration and in which varying degrees of progress have already been achieved are: (1) alcoholism, (2) juvenile delinquency, (3) mental health in the school and college, (4) accident prevention, and (5) the impact of urban and suburban life on mental health.

These program development activities, which have significance not only for the Institute's own program but also provide a focal point for nationwide interest in a particular problem area, are in part made possible and strengthened by the existence, within the NIMH, of the Mental Health Study Center, the Biometrics Branch, and the Publications and Reports Section.

Past Accomplishments

In general, the National Institute of Mental Health, since its establishment, has contributed significantly to almost every important development in the mental health field. It has served as the focal point for the Federal Government's activities in this field, and has used its resources to focus national attention on mental health problems, to expand and improve research efforts in all parts of the country, to train large numbers of additional professional people, and to help the various States and Territories as they sought to improve their own programs.

Some of the more outstanding examples of recent progress in the mental health field are:

... In 1950, 340 persons out of every 100,000 persons in the country were patients in a public mental hospital. By 1961, this rate had decreased until only 291 persons out of every 100,000 were patients in such hospitals, a decrease of 49 per 100,000 persons.

... In 1949, the average expenditure per patient in a public mental hospital was $1.72. In 1960, the average expenditure per patient day was $4.72.

... Following the discovery, in the mid-1950's, of the usefulness of the psychoactive drugs in controlling the symptoms of some of the mental disorders, the atmosphere of the public mental hospitals has been greatly improved. More and more hospitals have unlocked the doors of their wards and become "open" hospitals, and the number of patients released from mental hospitals after a relatively short period of treatment has been greatly increased.

... The concern of the general public for the care and treatment of the mentally ill has been demonstrated in very concrete ways: thousands of citizens now work, as volunteers, in schools for the retarded and hospitals for the mentally ill.

... A great deal of experimentation leading to the development of new types of mental health services has occurred. These may be grouped together under the term "community" psychiatry,

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...A great deal of experimentation leading to the development of new types of mental health services has occurred. These may be grouped together under the term "community" psychiatry, and include services that provide for less than round-the-clock hospitalization--day and night hospitals, emergency psychiatric services, and aftercare and rehabilitation services.

In 1946, there were only 471 outpatient psychiatric clinics in the entire country. By 1960, this number had grown to 1,505.

...While in earlier years most general hospitals did not admit patients with a psychiatric diagnosis, by 1958 more patients with a psychiatric diagnosis were admitted to general hospitals than to public mental hospitals.

...The number of persons working in the mental health field has greatly increased since 1948. By 1962, the training programs of the NIMH had grown until 4,570 persons were being supported on trainee stipends in 305 training programs.

...Since the close of World War II, the amount of research being done in the mental field has greatly expanded. Between

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... Since the close of World War II, the amount of research being done in the mental health field has greatly expanded. Between the fiscal years 1948 and 1960, the NIMH made 4,044 research grant awards, for a total expenditure of over $76,000,000. Funds available for NIMH research grants have increased steadily, and appropriations for research grants in fiscal 1963 were $56,102,000.

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Table 1

Personnel in permanent positions as of 12/31/62

Research	387
Collaborative studies	150
Training activities	53
Professional and technical assistance	135
Review and approval	147
Program direction	31
Total	903

Table 2

1963 Appropriation

Grants:		
Research		$55,635,000
Fellowships		5,940,000
Training		49,373,000
State control		10,950,000
Total grants		121,898,000
Direct operations:		
Research	476	10,222,000
Collaborative studies	170	3,842,000
Training activities	55	596,000
Professional and technical assistance	183	2,926,000
Review and approval	203	2,917,000
Program direction	40	799,000
Total direct operation	1,127	21,302,000
Transfers	1	399,000
Total appropriation	1,128	143,599,000

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

Legal Basis

The story of the National Institute of Neurological Diseases and Blindness (NINDB) begins after World War II as the story of people devoted to a little-known but deeply humanitarian goal. Their dream was the conquest, through research, on "the cause, prevention, and methods of diagnosis," of the more than 200 neurological ailments. Some of these had been ghosts in the closet for centuries.

Epilepsy, mental retardation, cerebral palsy, and Parkinson's disease, to name a few neurological ailments, were not popular causes at that time, but they afflicted millions in the United States. Among the sensory disorders, blindness aroused public sympathy, but all too little support for active research. Deafness, and major hearing and speech defects handicapped even more persons than blindness, but support of research in this field had even less popular appeal.

In the five years leading to 1950, a number of voluntary health organizations grew up in the field of neurological disorders. Some remained independent; others joined organizations of longer standing. They petitioned Congress to establish separate institutes in each of their ailments.

However, persuasion by certain legislators and the Surgeon General of the Public Health Service led the petitioners to consolidate their interests in a request for one institute to deal with all neurological and sensory disease problems.

This united approach appealed to Congress, which passed an Act creating the desired new Institute within the framework of the Public Health Service and its main research arm, the already existing National Institutes of Health.

Public Law 692, of the 81st Congress: "To improve the health of the people of the United States . . . the Surgeon General shall establish in the Public Health Service . . . an institute for research on neurological diseases (including epilepsy, cerebral palsy, and multiple sclerosis) and blindness." Excerpt, Sec. 431 (a). This Act of the 81st Congress was signed on August 15, 1950, by the President into Public Law 692. Here was the legal birth of the National Institute of Neurological Diseases and Blindness, often called NINDB.

The name could be simpler: some people call NINDB "The Neurology Institute." The name could be more exact, because the nerve affliction of blindness is spelled out, but the gravely important hearing and speech disorders are not named, although a real concern of NINDB. Sometimes the Institute speaks of its obligation for research in "neurological and sensory disorders" in order to include both blindness and deafness.

History and Development

The NINDB, authorized by Congress in 1950, received its first budget of $1,232,253 in 1951, most of these funds representing transfer of research projects in neurological and ophthalmic research from other Institutes and the Division of Research Grants. Also in this same year,

the first NINDB director was named, and though only about $40,000 was allocated for planning and administration, the actual programming for research and training was initiated on a broad scale.

Plans envisioned the opening of the Clinical Center in 1953 and inauguration of the Institute's intramural research program there, equipped and staffed through allocated funds. The program included research in local nutrition and metabolism of the brain, neurochemistry, pathology, neurophysiology, biophysics, bacteriology, and epidemiology.

In 1952 there was a slight increase in the budget. With limited resources, the program emphasis centered on providing support for specific research projects to be undertaken by the then available and trained investigators.

However, in 1953, the Institute was broken out as a budgetary line item. With a budget increased to $4,500,000, the Institute was then able to initiate a program in clinical investigation and appoint a Clinical Director and a Chief of Neurosurgery.

It was recognized early that research advances were dependent upon the availability of capable investigators. Therefore, a training program in neurology and ophthalmology, with emphasis on both clinical and basic sciences, was initiated in 1953. This program then expanded to include the training of investigators in chemistry and physics, and to orient them to the advantages of utilizing these techniques in developing knowledge of the structures and function of the nervous system.

In 1955, with additional increases in funds and space, a clinical investigations program in ophthalmology was established with a Chief of Ophthalmology appointed.

Growth of the Extramural Program closely paralleled the increase in total appropriations for the NINDB. Grants for graduate training of academic and research personnel in neurological and sensory sciences began in a very small way in 1952-3. Following the growth of the Institute, funds for training were doubled in 1957 and greatly accelerated by the expansion of training in neurology and ophthalmology and by the addition of training in otolaryngology and basic neurological sciences.

Field investigations initiated in 1957 were designed to support broad collaborative and cooperative clinical studies, field investigations, developmental projects, community studies and surveys, and pilot projects of a nature which would contribute to methods and procedures for the prevention, control, diagnosis, and treatment of neurological and sensory disorders.

The Intramural Program actually began operations in 1953, when approximately $1 million was allocated to direct research, both clinical and basic. With the gradual completion of the laboratory and patient facilities of the Clinical Center, and the staffing of both areas, the Intramural Program has developed steadily to an annual operating level of approximately $7 million. With the completion of the NIMH-NINDB

Laboratory Research Facility, for which funds were appropriated in fiscal 1961 and planning is now underway, another major advance in the program will be possible.

The aim of NINDB clinical research is to improve the diagnosis, treatment, and prevention of neurological and sensory disorders. Patients who are admitted to the Clinical Center are participating in current research projects which involve studies of the clinical manifestations of a wide variety of such disorders. Some of these conditions are also being investigated in parallel or related studies in animals. These studies include electrophysiological, biochemical, pharmacological, microbiological, and pathological studies, which may be correlated with clinical findings.

In addition to clinical research, a basic research program encompasses the fields of anatomy, physiology, biochemistry, pharmacology, psychology, pathology, sociology, molecular biology, biophysics, and allied disciplines relating to the brain and nervous system.

The concept of organizing a multi-institutional collaborative project for investigating neurological deficits associated with perinatal, natal, and postnatal damage to the nervous system dates back to 1953. In 1954 preliminary plans were revealed to the Appropriations Subcommittees. A detailed analysis of objectives and study design was made in 1957; work was carried forward on the development of methods of examination for the study and the organizational structure of the

central office; and the organizational structure of the central office and collaborating institutions was laid down. The pretest phase was launched in January 1958, the first case actually registered in the main phase of the Project in January 1959. By October 1962, over 30,000 mothers and more than 25,000 babies were participating in the program expected to reach its initial goal of 50,000 pregnancies by January 1, 1965. The program entails an extended follow-up continuing through school age.

Under the broad Institute program of Collaborative Research are other programs important to neurological and sensory research: the Epidemiology Branch, the Biometrics Branch, the Laboratory of Perinatal Physiology in Puerto Rico, and the Special Projects Branch.

A program of professional and technical assistance was envisioned in 1958 and funds were made available in the Institute's budget for the fiscal year 1962. The program was established in the Division of Chronic Diseases in the Bureau of State Services with arrangements for close cooperation and general advisory aid from the Institute. This neurological and sensory disease program was charged with collecting and developing information relating to neurological and sensory disorders and disseminating the information to professional and lay individuals and groups to foster the widespread application of new research findings. This program will have its own appropriation beginning fiscal year 1964.

Funds made available in the years since NINDB was founded have made possible an extensive research program resulting in a number of dramatic findings, a few of which illustrate the broad scope of the Institute's research program:

Retrolental fibroplasia, which caused blindness in thousands of prematures over a ten-year period, has been practically eliminated through research findings growing out of a cooperative study largely supported by the Institute. The study found the disorder could be prevented by reducing the concentration of oxygen administered to prematures.

Cataract operations have been greatly facilitated by the use of an enzyme which softens the supporting ligaments of the eye lens. Important advances have been made in the diagnosis and management of glaucoma. The tonometric examination of the eye, performed at yearly intervals, is capable of making possible early diagnosis of individuals destined to lose their vision through glaucoma and use of new drugs is preserving vision in a large percent of diagnosed cases.

The development of corneal transplantation is restoring sight to many with scarred corneas. New means of preservation are making it possible for donor eyes to be kept in viable condition for long periods of time, even in shipment. More recently, experiments with plastic substitutes may make the use of donated eyes unnecessary.

Important research advances have also occurred in speech and hearing. Control of infections of the ear in childhood has reduced

the frequency of middle ear deafness. It is now possible to restore an eardrum destroyed by disease. Among adults, most dramatic has been the surgical restoration of hearing after years of deafness produced by otosclerosis.

Mental retardation is a leader in the field of research today and promising results are appearing in numerous phases. It has been found that familial forms of cretinism frequently can be prevented by thyroid hormone treatment during pregnancy of women known to be predisposed to this condition. A new disorder affecting the central nervous system, called "Maple Sugar Urine Disease," has been identified. This disease of children is attributed to an inborn error of metabolism resulting in severe neurological impairments often leading to death. Early diagnosis and the development of the proper replacement therapy are of particular importance. A new screening test has been developed which can detect phenylketonuria (PKU), another metabolic disorder, within the first week of life. Kernicterus, an important type of mental retardation and cerebral palsy, has been largely attributed to Rh blood incompatibilities between the mother and the fetus. Grantees have reported the mechanism through which the bilirubin produces the brain damage and have shown it can often be prevented or reduced by use of the umbilical cord for effective exchange transfusion.

Understanding relationships between asphyxia and neurological deficits is a primary goal of the collaborative program carried on by the Institute and the University of Puerto Rico in the Laboratory of Perinatal Physiology. Studies are being made to determine harmful

factors which produce injury to the newborn and methods of counteracting these harmful effects. Infant monkeys asphyxiated and resuscitated at birth have been found to develop various degrees of neuromotor and behavioral handicaps, including symptoms comparable to cerebral palsy, epilepsy, deafness, and mental retardation.

Not only have the broad plans envisioned in 1952 come into reality as the Institute has continued to grow and expand, but many new fields and concepts have been added to the program. This year 278 research projects are underway in the Bethesda laboratories and 1384 extramural research projects are being supported. In addition to significant research advances, the Institute's training grant program has made notable progress toward meeting the urgent need for trained investigators in neurological and sensory disease research.

Need for Neurological and Sensory Research

The brain, the body's most intricate, sensitive, and versatile organ has for centuries aroused unusual curiosity and study. Yet it remains a major enigma in modern medical science. Wider understanding of the amazingly varied activities of the brain and nervous system holds the key to increased prevention and cure of disabling chronic neurological and sensory disorders.

It is estimated that more than 10 million persons in the United States suffer from some chronic disabling neurological or sensory disorder, ranging from speech defects and hearing problems to disorders

causing crippling and death. Cerebrovascular disorders, for example, rank as the third leading cause of death in the United States.

In most of these disorders of the central nervous system, the manifestations are multiple and complex, and the cause is obscure or little understood. Moreover, many of the essential facts underlying the anatomy and chemistry of the nervous system are still unknown.

The incredibly intricate order of cells in the living human brain presents a great challenge to science. More unanswered questions exist about the brain and its workings than about any other organ of the human body. Because it is both highly complex and inaccessible, the brain yields slowly to scientific exploration. Gradually, however, scientists are acquiring greater understanding of how the billions of nerve cells, woven into a network of thousands of nerves, work together to accomplish their vast task. More facts are also being uncovered about causes of damage to the brain and central nervous system, and the reaction of nervous tissue to such injury.

Although some neurological impairments are well known to the public, others are largely or completely unfamiliar. Among the hundreds of neurological disabilities are cerebral palsy, multiple sclerosis, muscular dystrophy, epilepsy, strokes (intracranial lesions of vascular origin), brain tumors, mental retardation, blindness, deafness, and speech defects. Others, such as Freidrich's ataxia, Huntington's chorea, Werdnig-Hoffman's disease, and von Recklinghausen's disease, are largely or completely

unfamiliar; some are killers and cripplers. All in all, according to the National Committee for Research on Neurological Disorders, more than 200 clinical entities, which may be called neurological disabilities, are associated with dysfunction, disease, or injury of the nervous system, the brain, the spinal cord, and their peripheral neuromuscular connections.

A serious problem in overcoming neurological and sensory impairments is the lack of skilled manpower. Less than 1 percent of all certified physicians are neurologists. In private practice, there are 531 certified neurologists and in full-time teaching or research, 214. Clearly, the specialty of neurology is vastly undermanned when it is considered that at least 6 percent of the nation's population suffers from neurological impairments, 12 percent of all deaths are caused by neurological disease, and 90 percent of all totally disabled dependents receiving Social Security benefits suffer from neurological disorders.

During the early decades of this century, and in fact until the Congress launched the Institute's program, the study of the nervous system was becoming almost extinct. Lack of interest, the complexity of the problem, inadequate methodologies, and an emphasis on the behavioral disciplines, had all served to create a shift of emphasis away from the exacting demands of the neurological sciences.

The training program of the Neurology Institute has produced striking results in curbing the drift away from the neurological sciences, even though the supply of well-trained professional personnel (certified

neurologists, neurosurgeons, ophthalmologists, and otolaryngologists) is still inadequate to meet the tremendous demand. It is encouraging, however, that the number of supported training programs in the neurological sciences increased from 15 in 1954 to over 120 in 1962. In the past 2 years alone, the number of trainees in clinical and basic neurology and in neurosurgery has increased from 390 to 579.

A continuing rise in the number of certified specialists in private practice, as well as in full-time teaching or research, holds the key to accelerated progress in neurological and sensory research. Only with enough trained investigators and practitioners can greater knowledge be obtained of the underlying structure and function of the brain, nervous, and sensory systems. Such knowledge is essential to prevention and treatment of some of mankind's oldest disorders.

Organization and Staffing

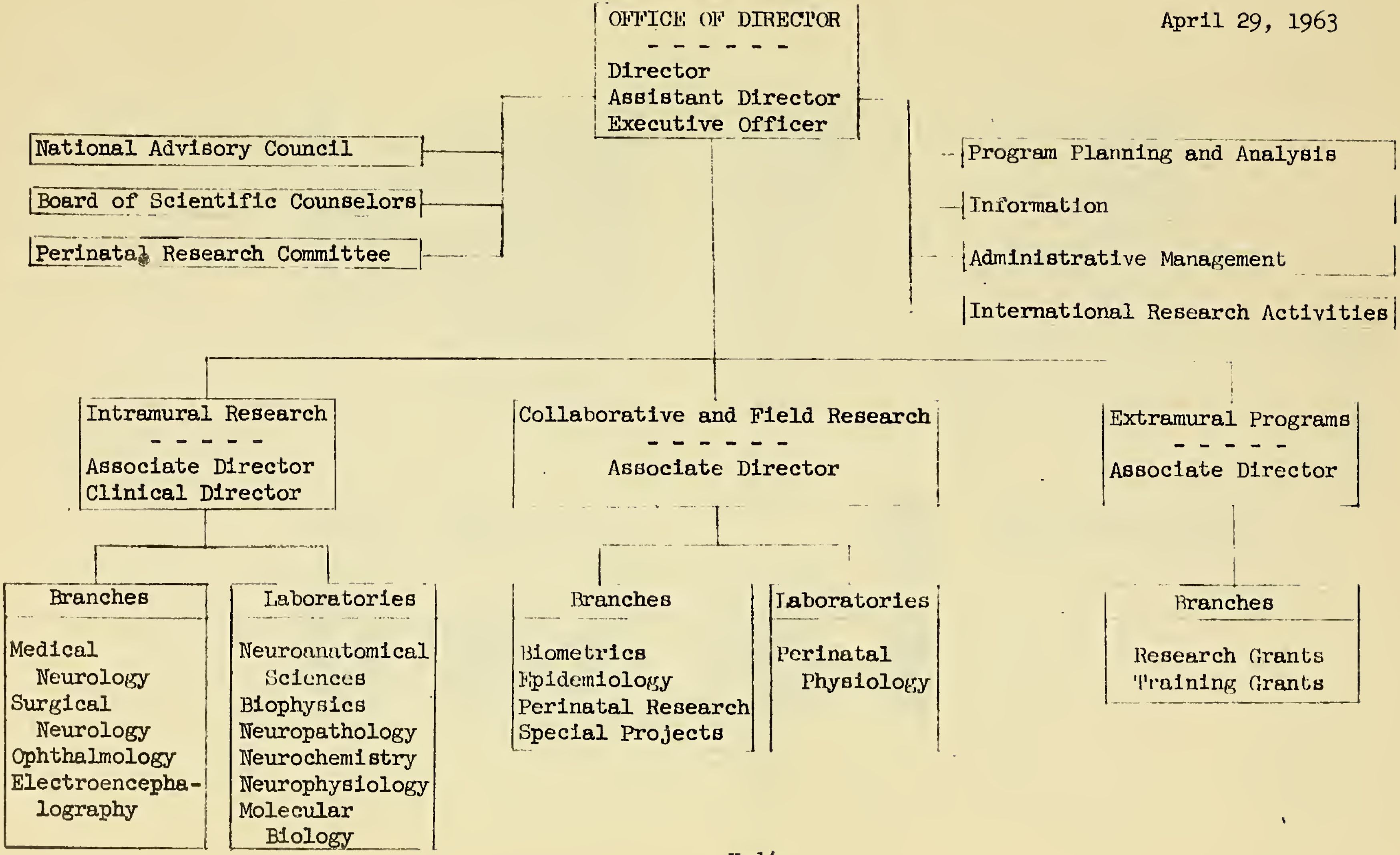
The National Institute of Neurological Diseases and Blindness is responsible for conducting, fostering, and coordinating research on the causes, prevention, diagnosis, and treatment of the neurological disorders, as well as conducting basic research in related scientific disciplines. In fulfilling these responsibilities, the Institute: (1) administers a program of grants-in-aid of research to public and private institutions and individuals in fields related to its areas of interest, including research project, program project, center, and research facilities construction grants; (2) administers a program of training grants and awards to increase the availability of trained professional research

manpower in areas related to the program responsibilities of the Institute; (3) conducts a diversified program of intramural and collaborative research in its own laboratories, branches, and clinics; (4) provides leadership, counsel, technical advice and guidance in developing and maintaining a nationwide research and research training effort in the area of its program responsibilities; and (5) collects and reviews neurological and sensory disease research findings of Institute scientists, grantees, and other investigators, and selects appropriate information to disseminate to the scientific community, and to the public; cooperates with the Division of Chronic Diseases, Bureau of State Services in their program for gathering and disseminating informational material prepared for the education and information of professional and lay individuals and groups to foster the widespread application of new research findings.

The responsibilities of the Institute are executed through the Offices of the Institute Director and the Associate Directors for Extramural Programs, Collaborative and Field Research, and Intramural Research as shown on the attached organizational chart:

NINDB ORGANIZATION CHART

April 29, 1963



Personnel
(as of 12/31/62)

	Positions
Professional.............	168
Technical................	133
Supporting:	
Administrative.........	105
Technical..............	196
Total....................	602

Budget

	1963 Appropriation	
	Pos.	Amount
Grants:		
Research...............		$51,232,000
Fellowships............		2,023,000
Training...............		13,767,000
Total, grants........		67,022,000
Direct Operations:		
Research...............	277	6,716,000
Collaborative studies..	330	3,851,000
Training activities....	7	75,000
Professional and technical assistance.	55	3,800,000
Review and approval....	100	1,594,000
Program direction......	35	448,000
Total, direct operations.........	804	16,484,000
Total Appropriation......	804	83,506,000

Intramural Research

The Intramural Research Program of the Neurology Institute has been active for nine and a half years of the eleven years of which the Institute has been in existence.

The program now comprises four clinical branches (Medical Neurology, Surgical Neurology, Ophthalmology, and Electroencephalography) and six basic laboratories (Neuroanatomical Sciences, Neuropathology, Neurophysiology, Biophysics, Neurochemistry, and Molecular Biology). Presently there are about 100 scientists, who have developed a broad program to investigate the basic characteristics of the nervous system, and its diseases.

As the program has developed, the focus of the basic investigations has been the functioning element of the nervous system--the neuron. The physical structure of the neuron, and the physical and chemical changes which accompany nervous activity are of fundamental importance to our knowledge of nervous activity. The central objective of the Biophysics Laboratory is to understand the nature and implications of the initiation and propagation of the nerve impulse

Scientists in the Laboratory of Biophysics have led in the development of a technique whereby the electrical current movement of the chemical ions across the delicate nerve membrane can be studied. In the past decade, this Laboratory in combination with laboratories in England have brought forth an imposing amount of data to confirm the ionic theory of neural transmission.

A major interest of the Laboratory of Neurophysiology has been determining how information reaching a nerve cell along different nervous pathways is integrated by the cell body and its dendrites and how this controls the cell's activity. Efforts have been directed toward various phases of this integration of incoming information. For example, a study has been made of the interaction of excitatory and inhibitory processes as they arrive at a single nerve cell. By following the electrical potentials generated in and around cells by their own activity and by incoming information, it has been possible to determine in part how a nerve cells works.

The program of the Laboratory of Neurochemistry has been concerned with the nature of the structural components of neural tissues and cells and with how these structural components subserve the characteristic specialized functions of such cells. Emphasis is being placed on elucidation of the chemical structure, biosynthesis, catabolism, and functional significance of the more complex lipid compounds of sphingomyelin, cerebrosides and gangliosides--the essential building materials of nervous tissue.

The structure and synthesis of various lipids has an importance to neurology because of the vast amount of lipids in the central nervous system. The Institute's Laboratory of Neurochemistry has furnished significant knowledge concerning the biosynthesis of these compounds and was the first to synthesize one of them--sphingosine.

The relationship of neural lipid metabolism to the demyelinating diseases is also under active investigation. The indications that autoimmune phenomena may be involved in such diseases as multiple sclerosis are being examined by immunochemical techniques at both the clinical and experimental level. The latter involve use of tissue cultures of myelinating neurons to study factors promoting myelination, demyelination and prevention or reversal of such processes.

Since many of the neurological disorders are genetically determined, the Institute has initiated studies in this area of research. Discoveries in the past decade concerning the role of DNA in heredity and the demonstration that viruses infect bacteria by the injection of pure DNA, have initiated the field of molecular biology.

The Laboratory of Molecular Biology was newly established in April 1962 and is now actively working on problems fundamental to the understanding of the structure and alteration of hereditary material, the synthesis of protein, and the control of enzyme formation.

During the past decade, the resolution of the electron microscope has now approached the level at which the chemist and the microscopist may join in so-called "molecular anatomy". Until the perfusion technique, using osmium oxide, was developed in the Laboratory of Neuroanatomical Sciences, it was difficult to study the central nervous system of any animal by electron microscopy. Many of the initial studies that confirmed the existence of the cell membrane were conducted here.

The precise structure of the sympathetic nerve endings on smooth muscle fibers has been revealed for the first time by scientists in this laboratory. This program offers a precise morphological end-point that may permit us to assess the effects of a wide spectrum of drugs which affect the autonomic neuromuscular system, and to do this precisely at specific nerve endings.

A method has been perfected for the long term infusion of fluids into the circulation of chick embryos during embryonic development. This makes possible an accurate assessment of the effects of a wide spectrum of drugs, endocrine substances, and other biologically active materials on the course of development. Curare, and similar drugs, were infused into chick embryos in order to assess the effects of transient paralysis on joint development. In the absence of embryonic movement, clubfoot and similar congenital joint defects result.

The research objectives of the Laboratory of Neuropathology have been to test the validity of current basic concepts of tissue organization and to outline procedures for a more consistent and precise interpretation of the microscopical findings of experimental investigations.

Scientists in this laboratory have found that in addition to the normal structural differences between young adult and old animals, the reaction of an organism to an experiment will change with aging. The severity of reactive changes and intensity of recovery in motor neurons

were shown here for the first time to vary in young adult and older rabbits subjected to transection of a peripheral nerve.

In view of the continuous changes which were found to take place with aging, the effect of an experimental procedure on neurons can be correctly interpreted only by a comparison of neurons from identical regions in animals of known age. Further inquiry about the origin of morphologic changes may provide a basis for understanding functional impairments which are characteristic of senescence.

During the past years, many of the techniques used and developed in the basic laboratories have been utilized in investigations of disease in man.

The study of neuromuscular disease, for example, has involved the use and coordination of various modern research techniques, including histo- and cytochemistry, biochemistry, immunochemistry and electron microscopy, in addition to the established clinical and basic techniques which include clinical chemistry, electromyography, and histology. With these combined studies, certain groups of diseases, such as muscular dystrophy, have been found to consist of several different types with different basic characteristics and therefore, presumably necessitating different forms of treatment.

There is a continued search for better drugs for treating myasthenia gravis--a disease affecting the neuromuscular junction. Two lycoramine

compounds, which are derived from daffodil bulbs, were developed, tested in animals, given a limited clinical trial, and were found to have a certain value in the diagnosis and treatment of myasthenia gravis. The search for other useful compounds will be continued.

The Surgical Neurology Branch has made many advances in the surgical treatment of nervous diseases in the past years. During the past year, for example, a new method of brain cooling provides for a greater patient safety and technical efficiency during operations designed for the treatment of epilepsy, brain tumors and arteriovenous malformations. This type of brain cooling provides the surgeon with the same technical advantage that the more complicated methods previously available allowed: that is a reduction in the sensitivity of the brain tissue to surgery and the subsequent excision which may be required in the treatment of brain lesions. However, it affects only the part of the brain under treatment and exposure and does not affect the head or body as a whole, as was the case with previous methods of hypothermia.

In an experimental study of head injury, in which the head is subjected to a very rapid deceleration, significant changes in the blood vessel pattern immediately and shortly after the blow have been observed through the use of cineradiographic techniques. This is the first time that these have been used in conjunction with an experimental study of head injury, and they are revealing of cerebrovascular changes concomitant with concussion.

The Ophthalmology Branch is continuing studies of the electrical responses of the retina and brain of human subjects. These responses are recordable with new techniques in which general and special purpose digital computers are used which greatly increase the sensitivity of data acquisition and processing. Abnormality of the retina, as well as of the conductive pathways in the visual system, are now detectable and various forms of retinal degeneration can be diagnosed with certainty.

It was in this laboratory that the first electron microscope studies in human cataracts were carried out and different types separated. Here, also, was reported the first association of cataracts with long-term steroid therapy.

Basic investigations in this laboratory, including studies of the electrical activity and chemical reactions of the photoreceptors, have added immeasurably to our knowledge of how the visual process works.

The cause and treatment of glaucoma has been of continuing interest to scientists in this laboratory. A new approach to reduce the increase in intraocular pressure in glaucoma has been based on experimental studies on enzyme systems in the eye. In preliminary studies of some patients with certain forms of glaucoma, beneficial effects of an enzyme inhibitor was shown when surgical means failed to be of value.

In other experimental studies, the role which the intraocular vascular bed plays in the regulation of the intraocular pressure is being studied. The possibility of a circulating humoral agent in the blood which may influence the eye pressure is also being examined.

This laboratory has been critically examining suspected causes of uveitis, the baffling inflammation of the iris, choroid, or ciliary body which often leads to blindness. In clinical investigations of one type of uveitis a new antibiotic has been evaluated. The results indicated that the most benefit was obtained when this antibiotic was combined with usual chemotherapy.

In investigating the side effects of drugs it was found that a widely employed anti-malarial drug caused severe retinal degeneration, leading possibly to blindness. This has led to intensive studies on the course of the disease, the identification of its early stages, and to attempts to speed up the excretion of the drug.

The main research activity of the Electroencephalography (EEG) Branch has centered upon the problem of epilepsy. In the clinical field, information has been obtained about the pathological mechanisms that enable one side of the brain to influence the activity of the other side. These and other studies have been made possible by the use of a new, refined technique of chronically implanted cortical electrodes in man, which have been designed by our scientists.

By means of the same technique it has been possible to study for long periods, during nocturnal sleep, the electrical activity of a patient with a particularly severe form of temporal lobe epilepsy and to observe the changes which accompany the various phases of sleep, including dreaming.

Also, the EEG Branch has provided a valuable service function in conducting routine diagnostic EEG examinations for patients referred from the other Institutes.

The bulk of the intramural program has been advanced by the scientists on permanent assignment to NINDB. However, we cannot overlook the contribution of the many visiting scientists who have come to NIH, attracted by the unique facilities available and the high concentration of specialists from many fields. The stimulation resulting from their visits and their publications, based on work carried out while here, have been a significant contribution to our program.

Extramural Programs

The Extramural Research Program of the Institute is designed to stimulate and support scientific investigations in the neurological, sensory, communicative, and related fields. This program supports many of the Nation's foremost investigators in their efforts to prevent and cure disorders such as cerebral palsy, mental retardation, Parkinsonism, cerebrovascular diseases, epilepsy, multiple sclerosis, amyotrophic lateral sclerosis, muscular dystrophy, myasthenia gravis, encephalomyelitis, cataract, glaucoma, uveitis, and disorders of hearing and speech.

The Extramural Program is administered by an associate director of the Institute. Organizationally, there are two major extramural divisions: the research grants branch and the training grants branch.

The research grants branch has staff scientists who serve as liaison between the Institute and grantees and between the Institute and the study sections of the Division of Research Grants.

The training grants branch has four training committees to review applications for support. Two committees are in neurology, one in ophthalmology, and one in communicative disorders. Each of these training committees is staffed by an executive secretary, a full-time professional employee of the Institute who serves as liaison between the Institute and recipients of Institute training funds. The Institute also has staff personnel for the processing and management of grants.

Extramural activities have been expanding rapidly. In fiscal year 1962, the Institute was supporting 1,384 extramural research projects totalling $36,363,872. Training support amounted to $11,631,482. This included support for 192 training grants, 84 postdoctoral fellowships, 267 special fellowships, 31 career development awards, and 10 career awards.

The rapid expansion of the program and an increased number of well-trained investigators has made possible the Institute's support of basic and clinical research covering a wide range of problem areas. New approaches are continually being considered by the National Advisory Council of the Institute, and the research accomplishments reflect this diversity.

One important retrospective study of the obstetrical background of cerebral palsy, completed this year, again highlights the significance of prematurity as a cause of mental retardation and cerebral palsy. Of those children suffering from spastic paraplegia, more than half were premature. Twin pregnancy, mechanical birth trauma and asphyxia also were important factors.

Current research emphasizes the role of neonatal asphyxia as an important factor in mental retardation. It has been shown that a lowering of body temperature under certain circumstances may increase the body's tolerance to asphyxia by reducing oxygen requirements. Part of the damage produced by asphyxia has been demonstrated to be a result of ionic changes with acidity. Neutralization of these effects appears to reduce significantly the secondary effects of asphyxia.

Cerebrovascular disease is the greatest cause of death within the neurological disease category. Approximately 200,000 Americans die from it each year. The Institute has supported the attack on various aspects of this disease. For the last four years the Institute has been supporting a cooperative study of surgical therapy of aneurysms. These pouch-like enlargements, occurring in cerebral arteries, weaken the arterial walls and lead to rupture and, frequently, fatal hemorrhage. Seventeen laboratories are moving ahead with a program to evaluate various surgical and medical methods of treatment. Studies thus far show that surgery may be a superior form of treatment for men who have suffered rupture of an aneurysm of the middle cerebral artery.

In spite of advances in surgical techniques, a large proportion of cases of intracranial hemorrhage, especially those resulting from high blood pressure, are not amenable to surgery. A recent study of 312 patients treated with hypotensive drugs indicates that drug therapy has a significant effect in improving the survival rates of such patients.

Improved diagnostic procedures are aiding both surgical and medical therapy of cerebrovascular disease significantly. Diagnostic techniques for cerebral hemorrhages have been developed in angiography, while radioactive dyes are being used in locating arterial narrowing. Also, radioactive tracers are providing important information regarding the dynamics of blood flow and the regulation of cerebral circulation.

A joint subcommittee on cerebrovascular disease has been established by this Institute and the National Heart Institute to assure surveillance of this field. It has provided for a bibliography of cerebrovascular disease to keep investigators informed of current developments. The subcommittee also is planning the fourth cerebrovascular conference to discuss new research approaches in the areas of rheoencephalography, cerebral edema, controlled clinical trials and cerebral blood flow.

By using the epidemiologic approach, and by working through the World Federation of Neurology, the Institute has developed three separate collaborative studies on the pathology of cerebrovascular disease. These include studies of the large vessel at the base of the brain, the severity of arteriosclerotic changes, and studies of the structure of the wall of the blood vessel.

Important new advances have been made concerning the basic mechanisms responsible for epileptic seizures. For some time it has been known that irritant substances implanted under the surface of an animal's brain can produce irritation with resultant epilepsy. Recently, similar results have been produced by partial isolation of the cerebral cortex from the deeper structures beneath it. These observations provide a clue to the mechanism through which accidental injury of the brain or disease may lead to a seizure state.

In petit mal epilepsy, a strong genetic factor has been demonstrated which appears to depend upon certain characteristics of the nervous system present primarily between the ages of 7 to 14 years. The highest frequency for petit mal seizures occurs during these years.

Experimental and clinical investigations, coupled with basic investigations of the chemical changes observed in various seizure states, are leading to continued improvement of drug therapy. A wide variety of anticonvulsant agents is now available and each makes some slightly different contribution.

A relationship has been demonstrated between amyotrophic lateral sclerosis, a disease being studied on the island of Guam, and a form of Parkinsonism with dementia. This unusual combination offers further clues regarding the cause of Parkinson's disease which is common in the United States. Drug therapy is making possible a modification of the symptoms of Parkinsonism. By manipulating movement regulating centers

deep within the brain, surgeons are offering considerable relief to sufferers from this disease.

The Institute is directly involved in the development of a program for the study and detection of chronic and latent virus diseases of the central nervous system. In 1959 the Institute, together with the World Federation of Neurology, supported a symposium dealing with encephalitic diseases to increase scientific awareness of this problem. Interest also has been heightened by discoveries of latent viruses capable of lingering in the nervous systems of animals over months or years and leading to slowly progressive neurological damage.

Several important advances have been made concerning the cause of myasthenia gravis. For many years it has been known that tumors of the thymus gland were unusually common in patients with myasthenia gravis, and removal of such tumors, in some instances, was believed to be followed by remission of the disease. Since recent studies show that the thymus gland plays an important role in the immunological functions of the body, the existence of auto-sensitization in patients with myasthenia gravis is suspected.

The Institute this year has organized a collaborative study of therapy in which the initial investigation is concerned with the use of ACTH in certain limited cases of myasthenia gravis. This hormone, which has an important inhibiting effect on the immune responses of the body, is believed by some investigators to have a beneficial effect.

In addition to the traditional research projects, the Institute supports 16 broadly-based programs of research activity under the direction of teams of established investigators. These undertakings, known as program projects, are flexible in nature and usually involve the organized efforts of groups of investigators, especially where a multi-disciplinary approach is desirable. The areas of research involved include clinical neurological evaluation (both diagnostic and therapeutic), neurosurgical procedures, neurochemical and neuropharmacological studies, neuropathologic investigations, and clinical psychological and genetic studies. From the coordinated efforts of scientists in these areas, advances will be forthcoming in medical therapy, surgical management, and clinical evaluation as well as in the basic sciences.

A future goal is anticipated to be the development of regional, multi-institutional clinical research centers. At such centers, outstanding investigators from medical institutions in a geographic area could utilize necessarily complex and highly expensive facilities for research--facilities which would not be feasible for the exclusive use of scientists in only one institution.

The Institute has found it advisable to expand its program to utilize the best international resources which may be mutually beneficial in solving common neurological and sensory problems. One of the most important international programs is the support of so-called paired grants.

These grants are made to specific medical centers in this country to work cooperatively in a designated research area with an outstanding research center abroad. Ten paired grants are currently active or in the process of negotiation.

An international collaborative study of blood groups and chromosomes was initiated in 1962. This project involves the participation of laboratories in Sweden, Holland, France, Italy, England, and the United States. The ultimate goal of the studies is to provide additional knowledge for the mapping of certain genes on the chromosomes. International cooperation also is being enlisted in other epidemiologic investigations.

The training grant program of the Institute has begun to make notable contributions toward meeting research manpower needs in the areas of the neurological disorders as well as disorders of vision, hearing, equilibrium and communication. Institute-supported training centers are in operation for scientists wishing postdoctoral training in the clinical and preclinical research disciplines.

Several important developments in the training program have been initiated by the Institute this year. These include the establishment of support for: (1) training at the predoctoral level, (2) postdoctoral training at the advanced level, and (3) the initiation of new or improved training programs in neurology, ophthalmology, and otolaryngology at those medical institutions where such a need exists. The Institute

also has broadened the intent of its program to support the training of medical personnel for careers in organized community health services and public health, as well as for careers in research and academic medicine.

Although the number of neurologists, neurosurgeons, ophthalmologists, and otolaryngologists engaged in full-time teaching or research remains relatively small, the impact of Institute training programs is quite apparent. This year the number of full-time specialists in teaching and research in neurology increased from 139 to 214; in neurosurgery, from 58 to 90; in ophthalmology from 64 to 98, and in otolaryngology from 33 to 58. Thus, the Institute is beginning to meet the need for teaching personnel as a first step toward increasing the research manpower needed in these crucial areas.

Collaborative and Field Studies

The Institute has developed a group of full-time staff scientists who are available to work with investigators throughout the nation in a collaborative fashion. This group of intramural specialists complements the activities of cooperating scientists and provides consultation and even special services when necessary to round out a total program.

Collaborative and field studies are conducted within an organizational framework which includes the Perinatal Research Branch, Biometrics Branch, Epidemiology Branch, Special Projects Branch, and the Laboratory of Perinatal Physiology. Within the Perinatal Research Branch, there are

several sections: behavioral sciences, epidemiology and genetics, obstetrics, pathology, pediatric neurology, project services, statistical procedures and analysis, and virology.

The value of cooperative and collaborative research has been amply demonstrated over the past few years. The first example of a cooperative project at the institutional level concerned retrolental fibroplasia. Eighteen hospitals consolidated into a single effort to determine the role played by the administration of oxygen to premature babies in the production of retrolental fibroplasia. A rapid solution to this tragic blinding condition has led to almost complete disappearance of the disorder. The success of this and other ventures pointed to the need for the Institute to develop facilities for more active participation in this type of collaboration.

The collaborative perinatal project, officially known as the Collaborative Project for the Study of Cerebral Palsy, Mental Retardation and Other Neurological and Sensory Disorders of Childhood, came into being in 1957. A joint endeavor of the Institute and 15 medical centers, this study seeks to determine relationships between factors affecting some 50,000 women during pregnancy and the neurological and sensory disorders of their offsprings. The Institute's Perinatal Research Branch serves as staff and coordinating center and provides central services, including data processing, for the study.

The results of a rather extensive series of analyses will be reviewed by the collaborators in mid 1963. These analyses are expected to lead to increased flexibility and diversification of the activities to be encompassed within the project.

A major research advance from the section on virology has been the isolation and cultivation of the German measles or rubella virus, which can cause irreparable brain damage to a baby if contracted by the mother in early pregnancy. Joint efforts of scientists at the Neurology Institute and the National Institute of Allergy and Infectious Diseases contributed to this achievement which should accelerate the development of a preventable vaccine. The importance of a vaccine is emphasized by a recent report that birth defects occur in some 50 percent of live-born babies whose mothers had rubella during the first month of pregnancy and in about 20 percent of infants whose mothers were infected during the first three months of pregnancy.

The Institute's Laboratory of Perinatal Physiology parallels certain aspects of the collaborative perinatal project. By using primates and other animals, investigators in this laboratory are studying the relationships between various adverse factors during the prenatal life, birth, and early postnatal life and neurological disorders in the offspring. These investigators are located in Bethesda and Puerto Rico. They now direct two field colonies of free-ranging monkeys on islands in Puerto Rico and a caged colony in San Juan.

An experimental technique has been developed whereby the unborn monkey is delivered by caesarean section and subjected to a standardized period of experimental asphyxiation. Central nervous system damage was produced in all instances of 10 or more minutes asphyxiation. A consistent pattern of neuropathology has been demonstrated in the thalamus and brain stem. The relationship of the neurological injury to syndromes of cerebral palsy and mental retardation is so clear that there can be no doubt about asphyxia during birth as a major primary cause. The monkey brain-damaged at birth and postnatally bears a striking resemblance to the human infant under similar conditions.

The collaborative and field studies include investigations of several primitive populations on the Island of New Guinea. In one study Institute scientists and collaborators are investigating a chronic, progressive degenerative disease of the central nervous system. In this disease, called kuru, long-term transmission experiments to higher primates are being conducted in attempts to isolate a slow virus infection. Although slow virus infections have not as yet been demonstrated in man, there are striking neuropathological similarities and epidemiological analogies that exist between kuru in man and some slow virus infections in animals. These infections may be responsible for some of the chronic progressive disorders of the central nervous system of man.

In another group in New Guinea, there is a high incidence of a wide spectrum of congenital defects of central nervous system associated with

hyperendemic goiter. This group is being studied as means of understanding a wide array of nervous system defects, such as congenital deaf-mutism, and mental and motor abnormalities associated with cretinism.

The unusual frequency of amyotrophic lateral sclerosis (ALS), discovered in an epidemiological survey on Guam, is being studied further by Epidemiology and Genetics Branch of the Institute. ALS is responsible for approximately 10 percent of the deaths among the adult Chamorro population of Guam. Originally, ALS was thought to be a genetically determined, inherited disease. Recent investigations in this same area, however, have revealed that ALS is equally prevalent among the Carolinian population, a group not genetically related. Additional isolates of ALS have been discovered on the Kii Peninsula in Japan and more recently in an isolated region of New Guinea. It is possible that each of these populations represents an unusual genetic focus, but it is more likely that some environmental factor is responsible.

The Institute, in collaboration with the Patuxent Wildlife Research Center, recently initiated a new program specifically directed toward the investigation of latent infections. Certain degenerative diseases of the nervous system are known to occur in wild animals and may be infectious. Efforts will be made at Patuxent to isolate viruses which may be causing such human diseases as multiple sclerosis, chronic epidemic encephalitis (a form of Parkinsonism), kuru, amyotrophic lateral sclerosis, and certain forms of epilepsy of childhood. Specialized resources and, above all, the broad experience of the Fish and Wildlife

Service, Department of Interior, in gathering and handling wild animals, are critically important to this study.

The Biometrics Branch offers statistical consultation and service to investigators outside of the Institute as well as to clinical and basic research investigators in the Institute. The Branch also conducts research projects with other investigators concerning such topics as incidence of disease and environmental factors in disease.

As a result of the Biometrics Branch's determination to secure more adequate statistics on incidence and prevalence of blindness in the United States, it has been interested in improving blindness registers in the various states. This interest developed into the establishment in March 1962 of a Model Reporting Area for Blindness Statistics composed of the following eleven states: Connecticut, Delaware, Hawaii, Kansas, Louisiana, Massachusetts, New Hampshire, New Jersey, North Carolina, Rhode Island, and Vermont. Representatives from these states agreed to improve statistical reporting on blind persons and to stimulate research in the field of blindness.

In addition to direct participation in research, the Institute has been attempting to mobilize the efforts of groups of scientists for continual surveillance and direction of given fields, analysis of program need, encouragement and development of research programs, and to serve as a medium for scientific communication.

Among such special groups is an Institute-sponsored committee on drug evaluation with separate panels on certain major disease categories. These panels have developed improved techniques for evaluating drugs used to treat multiple sclerosis, Parkinsonism, headaches, and neuromuscular disorders. A pilot project for the evaluation of therapy on myasthenia gravis was launched this year.

Simultaneously, the roles and effects of drugs and teratogenic agents are being reassessed through the Institute's collaborative perinatal project and an independent perinatal project at the Kaiser Foundation Research Institute in California. Preliminary evidence from a large number of cases indicates that the average pregnant woman takes at least four different drugs during pregnancy. Controlled clinical trials with agents commonly used in pregnancy are already underway.

Development of each of these programs for evaluation of therapy requires the establishment of a central focus and coordination in data analysis. The Institute has attempted to develop these programs through its central office in Bethesda. To serve the national need adequately, however, it has become apparent that such foci should include not only the conduct of the field trials, but also responsibility for maintaining a complete overview of the field. This would include an information center through which the profession could be rapidly advised regarding available drugs, their efficacy, and the reported side effects. A program is now being developed to delegate the responsibility for such broad activities to regional university-based disease study centers.

The rapid accumulation of knowledge, especially during the past decade, together with the increased availability of trained personnel, now makes it possible to organize a broad attack against many unsolved neurological and sensory problems. To take advantage of these advances, the Institute has deveoped its various collaborative projects to bring together scientists from multiple research disciplines and many geographic areas. Through this effort, answers are being found to many problems whose causes until now have proven too complex to yield to investigation.

THE CLINICAL CENTER

The Clinical Center of the National Institutes of Health is a 14-story, 516-bed research hospital with twice as much space devoted to laboratories (approximately 1,100 laboratory units) as to patient care areas. Because "bench" scientists work here in close proximity to clinicians--often in collaboration with them--the Center has been called the place for "the complete look at the whole problem."

The Center was authorized by Congress specifically for medical research purposes, and does not offer general diagnostic and treatment services in the same sense as most hospitals. Patients are selected solely because they have a precise stage of an illness needed in a particular study being conducted by one of the Institutes. The patients are referred by their personal physician. Approximately 4,000 patients are admitted annually. While in the Clinical Center they receive, without charge to them, the best care known to medical science. When participation in a study is completed and their condition permits, patients are returned to the care of their own physicians; periodic follow-up examinations or treatments may be given for months or years. During the past five years, for example, the number of follow-up visits has increased from 24,842 in Fiscal Year 1959 to about 40,000 during Fiscal Year 1963.

Many years ago Public Health Service research was on a relatively small scale and largely devoted to studies conducted at the

sites of outbreaks of infectious diseases. However, as far back as 1911 it was recognized that lack of a clinical facility especially designed for research was hampering the effectiveness of Public Health Service investigations. Changing national health patterns led Congress to initiate in 1947 a large expansion of funds for both federal and nonfederal medical research; the parallel and progressive strengthening of NIH's own research activities in Bethesda made facilities for clinical study essential.

Design and construction of the Clinical Center (Legislative Ref: Sec. 301 and related provisions of the Public Health Service Act; 42 U.S.C. 241, et al.) were begun in 1948. The first patients were received in 1953.

The primary mission of the Clinical Center is to provide the specialized forms of hospital care necessary for the study of both normal and abnormal physical and emotional phenomena in patients. The Center is utilized by the clinical investigation programs of seven Institutes. The supporting services include nursing, dentistry, clinical pathology, nutrition, social work, diagnostic x-ray, anesthesiology, pharmacy, rehabilitation, medical records, blood bank, and other services found in a large, modern hospital.

In staffing this wide range of patient care services and furnishing employee health services to maintain on-the-job health of

about 10,000 NIH employees, the Clinical Center employs approximately 1,700 persons* and operates under a budget of about $13 million allocated from PHS appropriations.

In addition to the permanent staff, there is a constantly fluctuating population of guest scientists, clinical fellows, clinical associates, research associates, consultants, advisors, lecturers, and visitors, representing literally every professional category in the world of clinical medicine and biologically oriented science. Clinical fellows are appointed to those Institutes and professional departments where residency training, approved by an American Specialty Board, has been deveolped; for example, in psychiatry, periodontology, and clinical pathology. (An average of 1,000 persons with medical, scientific, and paramedical interests visit the Clinical Center each month; of these about 25 percent are from foreign countries and many of them represent ministries of health.)

Because some patients participate in long-term studies, every consideration has been given for their comfort. A solarium is available to patients on each floor; the Center operates a library for patients; there is a recreation hall with space for rolling beds and chairs; a chapel with interchangeable altar for different faiths; and special attention is given to occupational, recreational, and

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* See Table L-1

physical therapy as part of a broad program of rehabilitation.

To provide the baseline of health needed for certain studies, the Clinical Center has a normal volunteer control patient program. The selection of these patients is made primarily on a medical basis and they are recruited through special arrangements with certain universities, colleges, and church organizations. A healthy volunteer may experience minor discomfort, inconvenience, or boredom while participating in the research studies; but all procedures are carefully screened from the viewpoint of his safety and welfare.

The integrated laboratory-clinical investigation programs encompass many of the major causes of death and disability. This Federal hospital has gained stature during the ten years of operation and is recognized as one of the leading Centers of medical research. The research mission of the Clinical Center guides the activities of the several services beyond levels customary in most hospitals. For example, at the Clinical Center nurses find the time, equipment, instruction and guidance to function as effective members of the research team. Nursing research is an integral part of day-to-day patient-care activities. This type of study has helped in assessing the value of the latest, "tailor-made" electronic monitoring system for patients requiring close and constant physiological observations.

The Social Service Department also is involved in the developing sophistication of the total clinical research program. Increasingly, clinical investigators request social workers' collaboration in the study and treatment of the social components in chronic diseases.

The Anesthesiology Department in the Clinical Center must constantly perform complex and protracted procedures because of the utilization of heart-lung by-pass apparatus, hypothermia techniques, and the use of advanced electronic instrumentation for monitoring of vital functions in brain surgery, cardiac surgery, and radical surgical procedures for the extirpation of cancer.

These are but a few examples. Every Department of the Clinical Center could provide others: the demonstration of closed-circuit television as a teaching tool for professional education...advanced types of radiologic perception in the use of radioisotopes in "brain scan"...improved quality control automation of laboratory procedures in clinical pathology...application of electromyography as a dependable tool in evaluation of patients with neuromuscular disorders...formulation of radioactive pharmaceuticals for diagnosis and treatment...the use of plasmapheresis (the removal of blood for the purpose of obtaining a fractional component of the blood and returning the balance of the blood to the donor) for the supportive treatment of children with leukemia...development of new nutritional procedures for revised treatment of some metabolic diseases...the

application of environmental sanitation measures to control hospital infections and other hazards. These are but some examples of activities which are research today but will become routine tomorrow.

At the Clinical Center, constantly improving facilities add to optimism about the future. After years of intensive study and planning, the new surgical wing, encompassing many advantages possible through modern design and equipment, will be dedicated very soon. Meanwhile, advanced instrumentation in many areas has produced such useful devices as the whole-body radiation counter, the metabolic chamber, and other innovations of bioengineering. As one nurse commented after the first electronic heart-pacemakers were introduced to the Center several years ago: "These instruments are saving lives!"

Findings related to improved hospital utilization and patient care are communicated broadly as members of the staff lecture and publish frequently. The Clinical Center, itself, provides a large auditorium which is almost constantly in use for showing of medical motion pictures, orientation of new senior staff members of the Public Health Service, combined clinical staff conferences, national and international medical meetings, and evening lectures by world-renowed scientists.

TABLE L-1 Employment at the Clinical Center, National Institutes of Health Spring, 1963

Office of the Director Includes Immediate Office; Clinical & Professional Education; Information Svcs.; Executive Office; Patient Activities	50
Service Functions Administrative Svcs.; NIH Employee Health Svc. NIH Dental Svc.; Reception & Guide Svc; Transportation Svc.	72
Social Service Department	36
Professional Services Admission & Follow-up; Anesthesiology; Diagnostic X-ray; Dental; Clinical Pathology; Rehabilitation; Pharmacy; Medical Records; Blood Bank	390
Nursing Department Includes the following nursing services: Surgery; Follow-up; Cancer; Psychiatric; Heart; Arthritis; Allergy and Infectious Diseases; Neurology	588
Nutrition Department Patient Food Production; Floor Kitchens; Research Kitchens	222
Housekeeping Dry Cleaning Unit, Night Cleaning Unit, Elevator Operations	248
Laundry	51
Radiation Safety	16
Cafeteria	48
	1,721

DIVISION OF RESEARCH SERVICES

History and Development

The Division of Research Services provides facilities, equipment, and a wide variety of professional and technical services essential to the needs of the medical investigators and research administrators at NIH.

Until 1955 most of the basic functions now vested in the Division of Research Services were performed by several branches attached to the Office of the Director, NIH. In that year the Surgeon General approved the establishment of the Division of Research Services as a means of achieving more effective direction and control of the various research related services and of enabling them to respond more effectively to the growing and constantly changing needs of NIH research programs. The Surgeon General's action was taken under the authority of Section 301 of the Public Health Service Act as amended (42 USC 241).

As originally established, the Division consisted of six branches: Biometrics; Laboratory Aids; Plant Engineering; Research Facilities Planning; Sanitary Engineering; and Scientific Reports. The major elements in the evolution of the Division to its present organization (see attached chart) can perhaps best be described in terms of the changes that have taken place in the organization and functions of the original six branches. For the most part these changes have consisted of program adjustments within the Division in response to changing NIH requirements for the Division's services. In one or two instances, however, program functions have been detached from the Division in recognition of the fact that they were more appropriately the function of another NIH organizational entity.

Biometrics Branch

This Branch originally consisted of a Biometrics Section and a Statistical Processing Section. In 1959 the biometrics function was transferred to the National Heart Institute. In the following year, in response to the growing need of NIH for the application of computer technology to its biomedical research programs, the former Biometrics Branch was abolished, the Statistical Processing Section was reorganized as the Computation and Data Processing Branch, and plans were made for the acquisition of a Honeywell-800 computer. The major effect of these changes has been to convert the central data processing facility from a rather small EAM operation oriented toward the processing of administrative data to a large electronic computer facility, staffed with mathematicians and programmers, which is equipped to apply computer technology to extremely complex biomedical research problems and needs.

Laboratory Aids Branch

At the time of its establishment, this Branch had four major types of functions: (1) animal production, care, quarantine, issuance, and disease diagnosis; (2) sterilization and issuance of laboratory glassware; (3) production of culture media, solutions, and concentrates; and (4) the design and fabrication of special-purpose biomedical instruments. At the present time the Branch continues to perform the first three types of functions listed, but with modifications designed to meet the changing requirements of NIH research programs. As one example of program improvement the Branch has recently been assigned administrative responsibility for the NIH Animal Center at Poolesville, Maryland, where larger animals are maintained for research purposes.

In response to the growing demand of NIH investigators for highly sophisticated instruments, an Instrument Engineering and Development Branch was established in the Division in 1960 and assumed, on an enlarged scale, the instrumentation function originally vested in the Laboratory Aids Branch.

Plant Engineering Branch

There have been no essential changes in the functions of this Branch since the Division was established. Those functions include the operation and maintenance of the NIH physical plant and grounds; the alteration, repair, and extension of the existing facilities; and the administration and inspection of construction work performed by private contractors.

Research Facilities Planning Branch

This Branch was established to coordinate the planning and construction of new facilities on the NIH Reservation in Bethesda and at NIH field stations. To carry out this responsibility, the Branch employs a staff of design and construction engineers who work closely with the Public Buildings Service, architects, and contractors to insure that new facilities meet NIH program requirements. As a supplement to this basic function, a development program was formed within the Branch in 1960 under which short-term research and development engineering studies are conducted with a view to incorporating the latest design concepts in new NIH facilities.

Sanitary Engineering Branch

This Branch's principal objective of maintaining and improving environmental health and sanitation at NIH has not changed substantially since the Division was established. The Branch places special emphasis on identifying and solving sanitation, sanitary engineering, and bioengineering problems peculiar to a medical research and patient care environment. As part of a reorganization of Branch programs in 1961, whereby all sanitation and biological activities were grouped in one section and all engineering activities were grouped in another, the Branch name was changed to the Environmental Services Branch.

Scientific Reports Branch

This Branch has experienced a series of far-reaching changes since the Division was established. As originally organized, it consisted of six information-type sections: Special Events, Editorial, Publications and Reports, Library, Medical Arts, and Photographic. The Special Events function was transferred to the Clinical Center organization in 1958. In 1960 the Editorial Section and Publications and Reports Sections were transferred to the Office of Research Information, the Library Section was reorganized as the Library Branch within the

Division of Research Services, and the remaining Medical Arts Section and Photographic Section of the Scientific Reports Branch were reorganized as the Medical Arts and Photography Branch. Concurrent with these changes, the Scientific Reports Branch was abolished.

Organization and Personnel

As a result of the evolutionary stages traced above, the Division had by 1962 attained its present organization of an Office of the Chief and these eight branches: Computation and Data Processing; Environmental Services; Instrument Engineering and Development; Laboratory Aids; Library; Medical Arts and Photography; Plant Engineering; and Research Facilities Planning.

As of December 31, 1962, there were 1206 employees in the Division, including 1159 Civil Service personnel and 47 Commissioned Officers. These employees represented perhaps two-hundred different job categories, including engineers, veterinarians, chemists, mathematicians, programmers, instrument makers, glassblowers, librarians, translators, medical illustrators, photographers, landscape architects, electricians, painters, plumbers, and carpenters.

Budget Summary

The Division's budget for Fiscal Year 1963 is $13,260,597 apportioned as follows among the major program activities:

Office of the Chief	$ 303,700
Research Facilities Planning Branch	261,000
Laboratory Aids Branch	1,880,900
Instrument Engineering and Development Branch	867,397
Library Branch	551,000
Medical Arts and Photography Branch	528,000
Plant Engineering Branch	6,598,100
Environmental Services Branch	290,000
Computation and Data Processing Branch	1,980,500
Total	* $13,260,597

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* This figure includes $3,085,597 financed under the NIH Service and Supply Fund.

The Programs of the Division of Research Services

The programs of the Division of Research Services can be divided into two broad classifications: (1) those in direct support of NIH research programs and (2) indirect services related to the design construction, alteration, maintenance, and environment of the NIH physical plant and facilities.

Programs in Direct Support of Research

These include the development, design and fabrication of special purpose instruments; the production of bacterial and tissue culture media; the preparation of sterile glassware; the production of genetically controlled small research animals; the quarantine and conditioning of larger research animals; animal surgery and recovery; animal disease control; photographic services, including motion pictures and slide films of surgical procedures, clinical photography of patient surgery and gross pathology and specimens, and photomicrography and photomacrography; medical arts services, including medical illustration of surgical procedures and fabrication of plastic models to demonstrate clinical and pathological specimens; the development, testing or control of special environments needed for research or clinical purposes; and computation and data processing services in support of individual bio-medical research projects.

Programs related to NIH Facilities and General Environment

These include engineering liaison in the design and construction of new NIH facilities; engineering work directed toward the development of improved facilities and equipment for biomedical research; engineering and craft services required for the alteration and maintenance of the NIH plant and facilities; maintenance of the NIH grounds; and environmental services designed to maintain, protect and improve the health and well-being of NIH patients and employees and of laboratory animals used in NIH research programs.

As suggested by the above summary of DRS programs, the paramount objective of the Division is to provide a wide variety of scientific, technical, and engineering services essential to NIH programs. Since virtually all of these services are affected by changes in scope and direction of the Institute programs, the Division makes a continuing effort to keep informed of Institute plans and adjusts its organization, staffing, and functions accordingly. For example, the increased need for germfree and specific pathogen-free animals in biomedical research has led to the development of a program for the production of these animals, ultimately in substantial numbers, in the Laboratory Aids Branch.

Although the conduct of research is not a primary objective of DRS, a limited amount of research is permitted to the professional staff as a means of enabling the Division to recruit and retain high quality personnel. Moreover, it is often essential that research studies and investigations be carried out in the course of achieving program goals. Engineers, scientists, and technicians of the Division often work closely with Institute scientists on important research undertakings. For example, the electronics engineer works as a member of a research team in the development of new instruments, the plastics expert assists the surgeon by the molding of heart valves, the mathematician programs research problems for application on the computer, and the veterinarian and geneticist provide healthy animals of various strains and types for research. This close working relationship between the DRS and Institute scientific and technical staffs has proved quite fruitful in producing results of considerable significance to biomedical research. Typical of such results during 1962 were the development by an electronics engineer of the Instrument Engineering and Development Branch of a skin capacitance meter which measures the electrical capacitance of human skin, and shows promise as a screening tool for thyroid studies; the development, also by a Division electronics engineer, of a cartilage compressometer for the study of elastic properties of cartilage, which provides a new approach to research on the cause of diseases of the joints, such as osteoarthritis; and collaborative research between a veterinarian of the Laboatory Aids Branch and an investigator of the National Institute of Allergy and Infectious Diseases on a study of bovine ocular squamous carcinoma which led to the development of a method for reducing the recurrence of bovine ocular tumors.

Current Status of Division Programs

Computation and Data Processing

The Division seeks through its central data processing facility to achieve three basic objectives:

1. To provide a central computation and data processing service for NIH using electronic digital computers, electric accounting machinery, oscillogram scanner, plotters and other data processing equipment.

2. To provide expert mathematical and statistical assistance in the design, execution, and analysis of experiments and studies in the biomedical sciences.

3. To plan and conduct developmental work in the application of mathematics, statistics, and data processing methods to biomedical investigations.

Early this year the computer capacity was doubled by the acquisition of a second Honeywell-800 computer. Substantial progress was made during the past year in augmenting the programmer and mathematician staff. A study group representing NIH administration and Institute research programs recently devoted intensive effort to an analysis of the future orientation of computer applications at NIH. Of significance for the immediate future are plans for the rental of a small computer to be used in training research scientists in the art of computer use and a study by a group from the National Bureau of Standards to determine the long-range computer configuration necessary at NIH.

Environmental Services

The basic objective of the environmental services program of the Division as now organized is to promote satisfactory environmental conditions for personnel, animals, and equipment at NIH and at its field stations. Typical of the major continuing aspects of the program are the development of techniques for the evaluation and control of contamination in the patient care areas; development and application of standards for food service areas; and environmental engineering analyses of research laboratories utilizing biological, chemical, and radiological agents. Examples of progress made during the past year in the environmental area were the perfection of a transfer cylinder method for introducing sterile supplies into plastic germfree animal isolators and completion of an NIH-wide study of the handling and disposal of waste materials.

Medical Instrumentation Services

The principal objective of the Division in the area of medical instrumentation is to provide engineering and technical support to the intramural scientists at NIH through consultation and advice on engineering methods and instrumentation systems applicable to clinical and laboratory medical research, and through design, construction, and maintenance of non-standard scientific instruments. In addition, the Division's electronics engineers cooperate with biomedical engineering activities outside of NIH by disseminating information on new developments; supplying universities, research institutions, and commercial and non-profit organizations with engineering and technical knowledge and with recommendations on organizing biomedical support facilities; and stimulating interest among scientists, engineers, and students by publicizing the biomedical engineering field, its importance to medical progress, its career opportunities, and its education requirements.

Examples of the Division's biomedical instrumentation contribution within the past year include the development of a mobile monitor for a cardiac recovery room which detects and displays the patient's heart rate, electrocardiogram, and blood pressure, and a blood loss measurement system which permits the gravimetric measurement of blood lost during cardiac surgery. Also of significance was the expansion of research team participation (whereby Division engineers participate as members of Institute medical research teams) into the areas of biomagnetism and psycho-physiological studies.

Laboratory Services

The laboratory support services of the Division include quarantine, holding, treatment, surgery, and radiological services for larger research animals (such as dogs, cats, monkeys, sheep, horse, and cattle); production of high quality laboratory animals for research, including inbred strains and other special types; continuing surveillance, diagnosis, and investigation of the diseases of both large and small laboratory animals, and the development and application of disease prevention and control measures; production of all types of bacteriological and tissue culture media required in volume by NIH scientists; washing, sterilizing, and processing NIH laboratory glassware; and cage washing services for the Clinical Center.

Pilot studies for the breeding of germfree and specific pathogen-free animals were undertaken during the past year and limited numbers of these animals were issued to interested scientists for their evaluation. Recent tissue culture cell production on a small scale, mainly for use in quality control procedures, has provided a means by which the potential for future large scale production of such cells can be measured.

Although the construction of permanent buildings at the NIH Animal Center has not yet begun, quarantine activities for large animals were undertaken on a large scale at the Center during 1962 in existing farm buildings and other structures. For example, the average number of dogs under quarantine at the Center during the year was 228, compared with an average of 164 under quarantine at Bethesda.

Library Services

The Division's library services to the NIH research staff include the circulation of literature, the provision of reference and bibliographic assistance, the translation of foreign literature, and a photocopy service. In addition to providing these services through its own resources of people and literature, and through an interlibrary loan program, the Division supports and maintains professional relationships with specialized satellite libraries and reading rooms located in several Institute buildings and in NIH field operations, both here and abroad.

Significant steps presently being taken to improve the quality and scope of library services include inquiry into and exploitation of the newer aspects of the bibliographic process, known as documentation, which employ more refined methods of information handling, and the increased use of contracts for translating services as a means of reducing the backlog of requests for written translations and permitting the Division's translators to devote more time to oral translations.

Medical Arts and Photography Services

The medical arts and photographic services of the Division are designed to assist NIH laboratory and clinical investigators in the visual recording of biomedical phenomena and information and the dissemination of new knowledge to research and practitioner groups. Medical arts services include clinical drawings, general illustrations, exhibits, charts and graphs, varityping, publications design, silk screening, moulages, museum mountings, and development of specialized plastics materials. Photographic activities include medical photography, photomicrography and gross pathology, motion pictures, slides and slide sequences, and news photography.

The value of photography, art, exhibits, and drafting in the documentation and communication of results of scientific research programs is continually growing as new techniques, equipment, and materials become available. The Division makes a constant effort to search out technical developments in these fields and apply them to the recording of research information for subsequent utilization in publication, educational, and training activities. During the current year major emphasis is being placed on the design and preparation of animated sequences for films depicting research procedures and findings, and on the extension of photographic services to the reproduction of X-rays and aortograms.

Plant Engineering Services

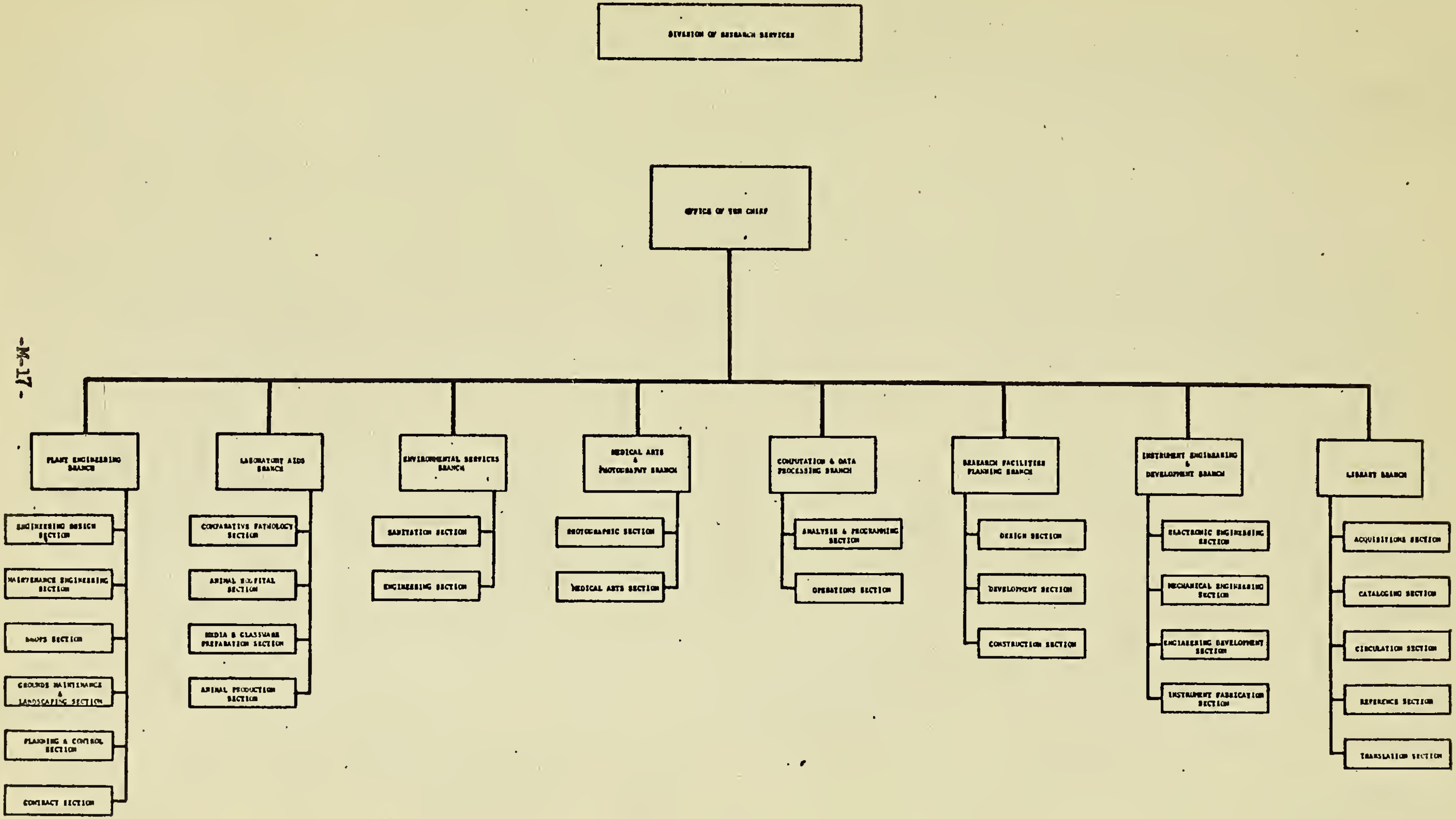
The Division provides engineering, craft, and laboring services necessary for the operation of the NIH buildings and the maintenance of the NIH grounds, and alters the physical plant as required to meet research or other program needs.

The operation, maintenance, and alteration of the research environment are functions to which the research program is highly sensitive. These functions have become more important at NIH as research equipment increases in complexity, and as environmental controls for research studies become increasingly demanding. During the past several years the Division has intensively studied NIH plant engineering requirements and has developed and implemented an organization designed to meet the needs of the Reservation. During the past year the final step in this development, that of establishing a planned and controlled preventive maintenance system, was completed. In addition to improved economy for individual services, the new program is providing immediate data on workload status, better maintenance of facilities, and the increased flexibility to meet research program needs. This service is directly related to the size of the research facility, and is therefore affected both by increases in space and by changes in the nature of research programs.

Research Facilities Planning Services

The planning and expediting of new research facilities for NIH requires continuing attention by a staff of engineers in the Division who assist the Institutes in the development of program needs and provide liaison between scientists, architects, Public Buildings Service officials, and contractors. The engineering staff also provides guidelines and criteria for the design of health research facilities in the form of brochures and special reports.

During 1962 the NIH design program involved 66 million dollars worth of construction, including fourteen building projects. In addition five major construction contracts were completed during the year.


DIVISION OF RESEARCH SERVICES
OFFICE OF THE CHIEF
PLANT ENGINEERING BRANCH
ENGINEERING DESIGN SECTION
MAINTENANCE ENGINEERING SECTION
SHOPS SECTION
GROUNDS MAINTENANCE & LANDSCAPING SECTION
PLANNING & CONTROL SECTION
CONTRACT SECTION
LABORATORY AIDS BRANCH
COMPARATIVE PATHOLOGY SECTION
ANIMAL HOSPITAL SECTION
MEDIA & CLASSWARE PREPARATION SECTION
ANIMAL PRODUCTION SECTION
ENVIRONMENTAL SERVICES BRANCH
SANITATION SECTION
ENGINEERING SECTION
MEDICAL ARTS & PHOTOGRAPHY BRANCH
PHOTOGRAPHIC SECTION
MEDICAL ARTS SECTION
COMPUTATION & DATA PROCESSING BRANCH
ANALYSIS & PROGRAMMING SECTION
OPERATIONS SECTION
RESEARCH FACILITIES PLANNING BRANCH
DESIGN SECTION
DEVELOPMENT SECTION
CONSTRUCTION SECTION
INSTRUMENT ENGINEERING & DEVELOPMENT BRANCH
ELECTRONIC ENGINEERING SECTION
MECHANICAL ENGINEERING SECTION
ENGINEERING DEVELOPMENT SECTION
INSTRUMENT FABRICATION SECTION
LIBRARY BRANCH
ACQUISITIONS SECTION
CATALOGING SECTION
CIRCULATION SECTION
REFERENCE SECTION
TRANSLATION SECTION

DIVISION OF RESEARCH FACILITIES AND RESOURCES

Introduction--Program Origins and Goals

The principal task of this Division, established by the Surgeon General of the Public Health Service on July 15, 1962, is to bring together under one operating unit a group of five extramural programs offering broad institutional or regional support for research in the health-related sciences. As its name implies the Division specializes in providing buildings, equipment, support for training people, and other resources needed by scientists and research clinicians--investigators who rely heavily upon modern scientific tools and methods to operate strong, interdisciplinary, multicategorical research programs.

Of the five programs assigned to DRFR, all of which were under way when the Division was established, the oldest provides for Health Research Facilities construction. It was originally established in the Division of Research Grants following passage of Public Law 835 in July 1956, which added Title VII to the Public Health Service Act. Since then, three additional acts have extended the program and increased the annual authorization of $30 million in available matching funds, to $50 million. Last date for submission of an application for such assistance under current legislation, is June 30, 1965, for funds which will be made available during Fiscal Year 1966. In spite of the increased authorization there is presently a backlog of more than $77 million in council-approved but unpaid grants.

. Second oldest Division program is that of the General Clinical Research Centers. These are multicategorical, multidepartmental, and multidisciplinary resources blending together in hitherto unobtainable discrete units the unique combination of preclinical and clinical sciences. As a result, the centers have given the nation a highly sophisticated broad program of clinical research. Not only have they raised the standards and expanded the national level of clinical research upon human disease, but each is providing a training ground of highest excellence for young physicians and scientists. There are now 41 active Clinical Research Centers in 23 States, the District of Columbia and Puerto Rico, and grants have been awarded for another 23 centers whose facilities are being renovated.

. The Animal Resources Program began in Fiscal Year 1961 with four Primate Centers under sponsorship of the Natioanl Heart Institute. These, and three others approved since, were originally established to aid research in cardiology. Their responsibility now is to provide facilities for a broad scope of scientific disciplines using primates in research. In DRFR the program will be expanded to include a national plan for providing many kinds of animals needed to cover all areas of specialized medical research. There is no intention, however, to compete with services already provided by established biological supply houses.

. Also under way in Division of General Medical Sciences during 1961, was a program of Special Research Resources providing modern computers and the expert personnel to operate them, in a limited number of areas where large programs of health-related research were in force. By December 31,

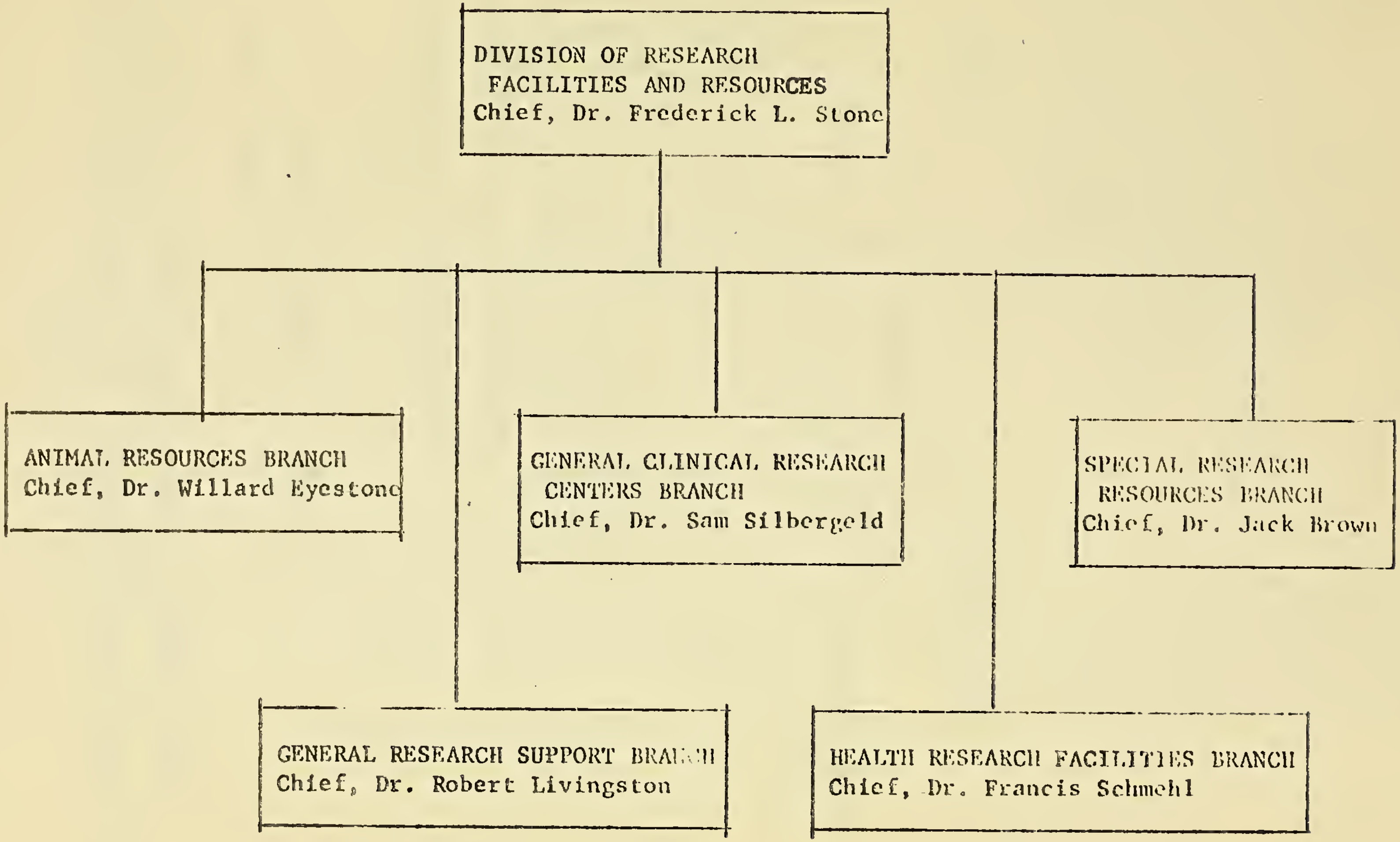
1961, grants had been awarded for five Computer Resources. By the end of 1962, 22 awards had been made, including one for a Biomedical Engineering Resource and five supplemental grants to the original five Computer Resources. Other types of Special Resources are in various stages of development.

. The General Research Support Grants program also orginated in DGMS in 1961. Its formation was in answer to a long-acknowledged need for specifically cultivating scientific excellence and improving the overall quality and strength of institutions in the conduct of health-related research and research training. Therefore, great latitude is permitted the qualifying institutions in determining the quality, content, emphasis and direction of such research activities. They are encouraged to capitalize on emerging oportunities, to explore new and unorthodox ideas, and to employ these funds for purposes which their judgment leads them to believe will contribute most effectively to the improvement of their total research capabilities. The first year's program included schools of medicine, dentistry, osteopathy and public health. Before the close of 1962, plans were well along to include schools of veterinary medicine, pharmacy, nursing, and separate research institutions, laboratories, centers, and other nonprofit research organizations also heavily engaged in health-related research.

Division Budget

The following table summarizes funds that were available to each of the Division programs during Fiscal Year 1963:

ORGANIZATION CHART


DIVISION OF RESEARCH FACILITIES AND RESOURCES
Chief, Dr. Frederick L. Stone
ANIMAL RESOURCES BRANCH
Chief, Dr. Willard Eyestone
GENERAL CLINICAL RESEARCH CENTERS BRANCH
Chief, Dr. Sam Silbergeld
SPECIAL RESEARCH RESOURCES BRANCH
Chief, Dr. Jack Brown
GENERAL RESEARCH SUPPORT BRANCH
Chief, Dr. Robert Livingston
HEALTH RESEARCH FACILITIES BRANCH
Chief, Dr. Francis Schmehl

General Clinical Research Centers	$ 33,500,000
General Research Support	30,000,000
Health Research Facilities	50,000,000
Animal Resources (including Primates)	5,120,000
Special Research Resources	6,000,000
Applications Review and Approval	839,000
Division Administration	242,000
Total	$125,701,000

Personnel

At the end of calendar year 1962, there were 77 persons assigned to DRFR, as follows:

Office of the Chief	18
Animal Resources Branch	5
General Clinical Research Centers Branch. . .	13
General Research Support Branch	8
Health Research Facilities Branch	29
Special Research Resources Branch	4
Total.	77

Division Programs in Detail

Health Research Facilities:

Under Title VII of the Public Health Service Act, DRFR's Health Research Facilities program provides up to one-half of construction costs

of buildings or portions of buildings devoted to research and related activities in the health sciences. In addition, the amount allowed may provide for up to half the cost of new equipment. In this way the program presents a powerful stimulus for institutions engaged in research to construct needed new facilities especially designed for modern biomedical research and to seek other funds to match those granted by the Federal Government. Their success in this respect is attested by the fact that over a seven-year period, some $230 million made available for construction has stimulated an investment in new and remodeled health-related research laboratories in buildings costing approximately $1 billion.

Current Program

The original Act established a National Advisory Council on Health Research Facilities. With the Surgeon General of the Public Health Service as chairman, this Council is comprised of medical, scientific and civic leaders familiar with aspects of planning and administering research institutions -- men and women whose experience enables them to assess broadly the needs for health research facilities and to judge the quality of the investigators and their research programs. It is the responsibility of the Council to evaluate all applications for health research facilities grants and to make recommendations to the Surgeon General concerning the awards and concerning various aspects of the program itself.

Eligible for awards are schools of medicine, dentistry, osteopathy, and public health; hospitals and other nonprofit institutions engaged in

or competent to engage in research. Among major purposes of the program are the improvement of the quality of research by expanding an institution's research capacity; and the promotion of an equitable distribution of research facilities throughout the Nation.

Although in some instances buildings can be renovated, in the long run, this expediency may cost more than new construction. Costs are exorbitant, for example, when some of the massive Gothic buildings common to many American campuses are torn apart for the installation of new wiring, plumbing, or air conditioning systems. Modern electronic equipment and new scientific techniques profoundly influence the design of modern buildings.

When Pasteur was developing his germ theory about one hundred years ago, (at a time when biomedical science was new) he used simple tools in his experiment--glass retorts and a microscope much less complicated than those used in high school chemistry today. Today's scientists use electron microscopes, some of which weigh more than a ton and for which special construction adjustments must be made. Modern computers need enormous amounts of power, and the larger ones require considerable space. Costly air conditioning systems must be designed so that dangerous bacteria are not circulated throughout a building and do not create an additional hazard by expelling active material into the outside air. Buildings must be planned so that laboratories with delicate electronic measuring equipment will not be near sources of vibration. These and many other considerations directly affecting the quality of research, dictate the

construction of new facilities rather than makeshift adaptations of old buildings.

Recent advances in the field of animal medicine offer another reason why new construction is preferable to renovation. Present-day research practices demand that animal quarters be given special consideration in design and construction. The condition of animals is a factor directly influencing the quality of research. Laboratory animals kept in overheated attics or damp basements, do not thrive. Monkeys are particularly susceptible to certain contagious diseases like tuberculosis and unless there are facilities for separating and maintaining sick animals apart from the healthy, an entire colony can be wiped out. This loss can be disastrous if a group of animals has been used in a series of experiments over a number of years. Though much remains to be done in the field of animal medicine, there is enough evidence about the proper skills and techniques of keeping research animals in good health, to provide standards for their adequate housing, to require forethought in preventive animal medicine and treatment, and to insist upon special construction and equipment.

Program Accomplishments and Procedures

During the six years of the program from Fiscal Years 1957 through 1962 and thus far through FY 1963, 1048 grants have been awarded to 373 institutions. The total amount of these awards is $229,984,925. Because

many institutions have more than one construction project for health research, the total number of projects supported by these awards (815) is more than double that of the number of institutions. In some instances, the award was part of the cost of an entire research building; in others it was for only the health-related section of a multi-purpose building.

When an institution applies for a health research facility grant, it submits an application together with floor plans, to the Health Research Facilities Branch where the request is reviewed and the plans are checked by Branch architects to make certain that the health-related areas of the building conform to application statements. A project-site visit then is made by one or more Council members and a staff member of the HRF Branch.

During the past six years, more than 1200 project-site visits have been made. Council members participated in 209 such visits during 1962, and in addition, devoted much time to the preparing of reports on their visits, to attendance at Council meetings, and to pre-Council-meeting reviews of application details. These reviews require careful judgments about the scientific productivity of investigators who will use the facility and about the scientific promise of their proposed projects and research program plans.

When assessing the research competence of an institution, Council members, most of whom are scientists, consider the past research record of its investigators, a record that in many instances is well known to

them. Indications of an investigator's scientific ability are the significance, quality, and recentness of published scientific papers, and the standards of the journals in which they appeared. Appearances on programs of important scientific meetings, appointments to outstanding committees and boards, and the favorable comments of colleagues, are other indications of a scientist's present and future capability.

It sometimes happens that after an institution has been awarded construction funds, problems develop. Some have difficulty in getting matching funds, or make changes in their total building program, or encounter various other delays that prevent use of the award money for a year or more. In such instances the institution is asked to relinquish the award so as to free these funds for another institution that is ready to begin construction. This accommodation between the research institutions of our country has been an effective mechanism for efficient program management.

Since the beginning of the program in 1957, 1435 applications have been submitted requesting more than $442,500,000. Each receives careful study by the Council which recommends to the Surgeon General the amount of Federal participation deemed appropriate. Some applications are not recommended for any award. Lack of qualified scientific staff in an applicant institution, the limited objectives of its health-related research program, or the absence of a conclusive demonstration of outright need, are the most common reasons for nonapproval.

When a building is ready for occupancy, a Health Research Facilities staff member visits the institution and checks the research facility to make certain that the amount of health-related research space supported by the grant conforms with what was outlined in the original floor plans. If before receiving its award, an institution changes its construction plans and reduces to a substantial degree the amount of space originally indicated, the revised plan must have PHS approval. If such changes are made after the funds have been awarded, the law provides that the institution shall refund an amount proportionate to the space reduction.

Part of the agreement with the institution requires that space supported by the award be used for health-related research and research training for at least ten years. A periodic check is made by staff members of the Branch to make certain that such requirements are met.

Program Potential

There will be many disappointed applicants in 1963. The demand, measured by Council-approved applications, has far outstripped available funds. Present program objectives call for supporting those regional or institutional groups which are planning to increase substantially their total research product. Some of the ways in which this is to be done call for new facilities for general clinical research centers, for strong support of the programmatic aims of the categorical institutes, for the addition of laboratories for research in mental health and mental retardation, for

computer centers, or for other special research resources. There is therefore, greater concern for the ultimate purpose of a proposed research facility -- particularly regarding whether or not the facility is absolutely essential to the continued development of those research programs that are of proven value in the search for new knowledge of disease and the methods of combatting disease.

National Need

To estimate the total national need for new research construction is a most difficult task. That such an unmet need exists and will continue, there is no doubt. A proper laboratory or clinic in which scientific investigation and study can take place is a major requirement. In importance it is second only to the need for personal financial support for the scientist himself. Is there a proper yardstick to measure this need?

For six years the amount of $30 million was set as the statutory limit of Federal matching support. After careful investigation of all applying institutions, there developed a considerable backlog of approved but unpaid awards. The statutory level is now at $50 million, and the backlog continues to grow.

Today, all of the $50 million Fiscal Year 1963 appropriation has been awarded. The unpaid backlog stands at almost $54 million. On the basis of pending, new, and deferred applications it is estimated that there will be a demand for around $70 million by June 30, at the outset of another fiscal year. In addition, there are a number of other institutions whose

plans are at a stage where they can estimate their construction costs.

Based upon experience, this means that more than $100 million additional could be used in Fiscal 1964 if it were available. On the premise that Federal participation inspires about five times as much construction spending on the part of local communities, the total investment figure for this type of construction could reach $750 million instead of an estimated $250 million which the present $50 million level of awards will make possible.

As medical research continues to expand (as it must if this country is to maintain a high standard of health for its increasing population) there will be demands for research facilities not only in new institutions but also in those which have already received one or more construction grants. Considering the fact that building construction takes a year or more, it is not unusual for quarters that seemed ample in the planning stages to be crowded soon after occupancy. In the future, more detailed consideration will have to be given to long-term construction needs.

General Clinical Research Centers Branch

Following recommendations by Congress in connection with the Fiscal 1960 Appropriations Act, the Public Health Service's General Clinical Research Centers program was started in the fall of 1959 as a responsibility of the NIH Division of General Medical Sciences. Such Centers support scientific investigators who share in a multidisciplinary, broad, integrated attack on a variety of medical problems. General Clinical Research Centers provide a stable organizational framework, an atmosphere

of common purpose linking research, teaching and healing; and an intellectual environment for research of high quality. Since the initial success of this program, additional funds have been made available for categorical clinical centers administered by the NIH categorical institutes.

Current program

As of May 1, 1963, 54 institutions in 27 States, the District of Columbia and Puerto Rico, have received assistance for 64 general clinical research centers with a total of 829 beds. Forty-one of these centers already are admitting research patients. Each is a discrete unit requiring extraordinary teamwork involving hospital authorities and staff, scientific and medical investigators and medical school administration. A great deal of cooperation is required on the part of each patient and very careful control is exercised over diet, medicines administered, special nursing attention, and many laboratory tests. This means, of course, a higher cost than is normal for ordinary hospital care. Adjacent to each center are special treatment rooms, diet kitchens, laboratory space, and specialized equipment. Highly trained personnel are requisite.

The term "General" as applied to these Clinical Centers allows for variety in the types of studies prevailing. Forty-nine are adult and three are mixed adult-children centers; 10 are for children only; one is solely for the study of premature infants; and one, (at Albert Einstein College of Medicine in New York City) is a center for acute problems,

studying shock, trauma, burns, sepsis, and pre- and postoperative patients. These differences directly affect not only the nature of each facility but also the equipment needed.

In size the centers range from 6 to 21 permanent beds, 0 to 7 core laboratories, and from about 2,000 gross square feet for the smallest, to 15,000 for the largest.

Many projects in the Centers are barely under way, but some results already published attest to the long-term value of the work being done. Disease categories investigated vary all the way from very common illnesses to the very rare. A patient at one center, for example, has a rare case of tumoral calcinosis. Large calcified tumors overlying the hips and shoulders presented Brazilian physicians in Rio de Janeiro with unusual diagnostic problems and the patient traveled to this country to enter a U. S. Clinical Research Center.

Some idea of the research accomplishments to be expected from General Clinical Research Centers activity can be gained from the following samples selected from a list of reported results:

- Muscular dystrophy has been linked to disturbances in metabolism by high-energy phosphates.
- Use of a transistorized "pacemaker" for stimulating the heart with radio waves has proven to be practical on seven patients with heart block.
- Certain lung cancers have been found to secrete a polypeptide which stimulates production of large quantities of adrenal cordical

steroids leading to severe Cushing's syndrome (a condition characterized by obesity, muscle wasting, skin atrophy, salt and water retention, etc.).

- Use of the artificial kidney has proven its ability not only to save lives but to maintain the health of selected patients for as long as two years.
- A method of determining the life span of human blood platelets was developed and applied to studies of blood banking methods and diseases associated with abnormal bleeding.
- It has been demonstrated that the anemia and hemolytic tendency of most patients with paroxysmal nocturnal hemoglobinuria (the periodic nightly appearance of red blood cells in the urine) can be corrected with iron and anabolic steroids.
- Development of a laboratory detection test for primary cancer of the kidney or bladder.

Within the Division of Research Facilities and Resources, the General Clinical Research Center program is administered by a staff of 13 persons including the Branch Chief and his professional, administrative and clerical assistants. Over and above the funds spent this year to maintain general Clinical centers already in existence, and to bring others into full research status, there are expected to be sufficient funds for grants with which to establish about 14 new ones. Currently under review, for example, is an application for a new type of General Clinical Research Center which will function as a maternal-child center. There are indications that other institutions are planning similar units,

especially those with considerable research activity related to studies of pregnancy and newborn children.

Special Research Resources Program

This program is designed to provide specialized research services or materials which, if attempted for one investigator, might be costly or difficult to justify and obtain. A basic requirement is, that funds be granted only for resources that are used by many investigators representing several disciplines in one or in many institutions within a region. In some instances, a Special Resource may serve scientists throughout the Nation.

Current Program

This program is now supporting 17 computer centers, for example, where vast amounts of data are processed in an incredibly short time, thus reducing the time lag between basic discoveries and their possible application to physical and mental diseases. While these computers now serve a useful purpose in certain aspects of biomedical research, a second phase of the program anticipates the development of computers designed especially for biomedical research -- useful for investigations in more sophisticated experiments. An important step toward this goal was taken recently in a cooperative arrangement with the Massachusetts Institute of Technology. There a "Center Development Office for Computer Technology in the Biomedical Sciences" has been set up, supported in part by the Special Research Resources program.

Program Results

Another established center has demonstrated admirably the effectiveness of the computer in research projects of the university medical center

where it is located, and has assisted also in research projects of several other institutions with whom cooperative arrangements were made. Among these are state mental hospitals, Veterans' Administration hospitals, public health departments, a number of medical schools and voluntary health agencies. Studies for which the center has been used include the monitoring of fetal heart sounds, factor analyses of surgical risks, air pollution, blood pressure and tranquilizers, the analysis of electroencephalographic records, correlation of ketosteroids to obesity, and the relation of therapy methods to types of cancer.

As more scientists become aware of the potential of computers for speeding research on problems once considered either too difficult or insoluble, the demand for computer centers is expected to increase rapidly. Reviewed at the November 1962 National Advisory Health Council meeting were 15 new applications; 13 for computers, one in biomedical engineering and one in the biomedical information field. Five were approved and one was deferred pending a future site visit.

Future Potential

Although program emphasis has thus far been preponderantly oriented toward developments in computer technology and computer usage for health-oriented research, it is expected that an increasing number of applications will feature other types of centers. These too, will be designed to aid institutions or regions totally, so that they can advance or improve their research capability and thus contribute powerfully to a combined multicategorical attack on the dread diseases.

A Special Research Resource in biomedical engineering, recently established at Northwestern University; for example, promises to establish a healthy academic climate where electronic, chemical, mechanical and other engineers can work with biomedical scientists to develop new concepts and instruments for advancing the study of human physiology; developing, for example, new methods of monitoring bodily functions. With the Federal Government currently spending some $2 billion for electronics research, largely for defense, and with tremendous progress being made in biomedicine, there is much to be gained through sponsoring a cross fertilization of these fields. One result already reported is a new technique employing acoustical principles to demonstrate how ultrasound waves can be used (much like x-radiation) to look into soft tissues of the body and study lesions of the heart and blood vessels.

Another type of resource to be explored, would aid research in communication science giving increased attention to methods of data processing, literature analysis, and information retrieval for both intramural and extramural programs of the NIH.

Other types of special research resources presently being discussed with institutions include centers for the production of large quantities of pure lines of mammalian cells and others for tissue and organ research.

Animal Resources

The Regional Primate Research Centers Program, formerly a responsibility of the National Heart Institute (NHI), was transferred to DRFR in July 1962 and forms the nucleus of the Division's Animal Resources Branch Program.

Present Program

It became apparent quite early that the need for using primates in research was great in a much broader scope, covering infectious diseases, reproductive physiology, cancer, arthritis, aging phenomena, etc. Consequently, these centers will now be a resource for all areas of biomedical research. Awards have been made for seven primate centers, three in the West at Beaverton, Ore., Seattle, Wash., and Davis, Calif.; and four in the East at Madison, Wisc., Boston, Mass., Atlanta, Ga., and New Orleans, La.; each to serve biomedical research institutions in its respective area.

Such centers will provide facilities especially designed to house certain species of primates and will include research laboratories where a resident staff as well as visiting scientists representing many disciplines can conduct research. It is expected that new facts will be learned concerning the biological characteristics of both healthy and diseased primates throughout their entire life span. In primates, scientists are discovering an increasing number of physiological and biochemical similarities to humans, thus enabling man to gain new knowledge with which to exercise increasing control over his own health and well-being. Centers already under way promise to add appreciably to the Nation's total research potential.

Future Potential

Although each center has its own program, six are regional centers committed to providing facilities for a broad scope of disciplines using primates in research. The seventh, at Davis, California, will be a National Primate Conditioning Center, committed to investigations on the

primate itself.

There have been many more applications for grants under this program than could be awarded. Each application was reviewed by the Primate Study Section of the National Institutes of Health and by the National Advisory Heart Council. Their recommendations for awards followed intensive reviews of the applications and visits by members of the Study Section and the staff to the applying institutions.

Criteria on which recommendations were based included the scientific calibre of the investigators, their experience in the field of primate research, and the scientific merit of the proposed research to be conducted in the centers. Because the center must be a resource for a community of scientists, the "host" institution must agree to make the facility and the primates available to visiting scientists and to share information of common interest with other primate centers.

After the awards were granted by the Surgeon General, the institutions began working with their architects and with staff members of what is now the Animal Resources Branch. Because the design of animal facilities is a highly specialized field and the design of primate centers a further refinement of that field, architects for all primate centers have sought guidance from the Branch staff, the members of which work closely with the architects throughout the planning and construction.

The conditions of the grants stipulate that, each year, operating costs of the centers are to be negotiated through the Animal Resources Branch staff up to the amount recommended by Council. Additional funds,

if needed, are sought through supplemental applications and are subject to Council review. Though the award recommends support for seven years, the Council periodically will conduct general reviews, at which time, if recommended, additional support up to seven years is granted. The operational support of these centers may include their total research program.

The present status of each of the primate centers is as follows:

Oregon Regional Primate Research Center

This was the first award of the Public Health Service primate center program, made in 1960 to the Medical Research Foundation of Oregon for construction and operation of a regional primate center. University of Oregon provides the scientific standards by which the center operates. The new facility, including unique out-door colony buildings, is on a large tract of land in Beaverton about 10 miles west of downtown Portland.

The initial research program orientation is on the physiology and biochemistry of the fetus and newborn primates, fetal skeletal biochemistry and growth, congenital anomalies, and cardiovascular physiology and pathology.

Regional Primate Research Center of the University of Washington

Grants have been awarded to the University of Washington for the construction and operation of a regional primate research center on the university campus at Seattle. The final construction plans are now in the drafting stage and construction is expected to begin soon.

Among key investigations to be conducted at the center will be studies in neurophysiology and electrophysiology, gastrointestinal physiology, skeletal and dental development, and obesity and dietary factors in cardiovascular diseases.

Wisconsin Regional Primate Research Center

Grants have been awarded to the University of Wisconsin for construction and operation of a primate research center adjacent to the present primate laboratory, on a site in the campus extension area. Construction on this facility began in October 1962.

Included in this facility will be an area where certain animals will be housed for many years to enable scientists to study them from birth to death, a life span that in rhesus monkeys is sometimes as long as 25 years. An extensive breeding program will be undertaken to provide a constant supply of young animals.

Among investigations to receive special emphasis at this center are studies on biochemical factors associated with mental retardation, postnatal development of the primate brain, hormonal factors in reproductive processes, and variables influencing the development of normal and abnormal behavior.

Yerkes Regional Primate Research Center of Emory University

Grants have been awarded to Emory University for construction and operation of a primate research center designed primarily for multidisciplinary study of the chimpanzee. Situated on the university campus, this center will assure the continuation and further development of the

psychobiological research of the Yerkes Laboratories of Primate Biology, Inc., owned by Emory University and now situated at Orange Park, Florida. Construction of the new facility is scheduled to begin in September 1963.

Areas of research emphasis of the new center will include studies on the relation of infant growth and experience to behavior in later life; physical, physiological, and psychological attributes of aged primates; brain functions; comparative studies on monkeys and other anthropoids; and effects of unusual environments and intense stimulation.

Delta Regional Primate Research Center

Grants have been awarded to Tulane University for construction and operation of a primate research center adjacent to Covington, Louisiana, about 26 miles from New Orleans. Plans are well along and construction is scheduled to begin late in 1963.

Research emphasis at this center will be on cardiovascular diseases, including experimental, dietary-induced atherosclerosis and hypertension in primates, other metabolic diseases, infectious diseases, radiobiological studies, and behavioral sciences.

New England Regional Primate Research Center

Grants have been awarded to the Harvard Medical School, acting in behalf of several Greater Boston and New England universities and medical institutions, for construction and operation of a regional primate research center on a 140 acre tract of land in Marlboro and Southboro, Massachusetts. Construction is scheduled to begin late in 1963.

The center will provide facilities and support for (1) investigations in bacteriology, physiology, nutrition, endocrinology, pathology, psychology and behavior in primates; and (2) the acquisition, breeding, and maintenance of a variety of primate species. In addition, the center will train professional and technical personnel in the care and management of primates in research laboratories, and will provide primates that meet special requirements for the research programs of the institutions cooperating in the center program.

National Primate Conditioning Center

Grants have been awarded to the University of California for construction and operation of a National Primate Conditioning Center at the University's campus at Davis, California. Construction is scheduled to begin late in 1963.

This center, possibly unique in the world, will serve as a national resource of studies on a wide variety of primates, principal consideration being given to suitable methods of animal transportation, and to ways of keeping primates in normal health as control groups for laboratory experiments. Other studies will focus on the suitability of various species for particular types of biomedical research. Breeding facilities will be developed to provide data on large-scale controlled production. The facilities will also be used for breeding animals of special genetic characteristics. A further activity of the Davis center will be to supply certain animals and animal materials to qualified scientists who require primates with special biological characteristics.

Future Potential

According to present schedules, all seven primate research centers will be in operation by the end of 1964. Once they are in operation, there will be a continuing liaison between the centers and the staff of the Animal Resources Branch. Two major responsibilities in this liaison are the annual negotiations of budgets for operating costs which consider among other factors, funds received for research projects from other sources; and a pooling and dissemination of information of common interest to all centers and to the scientific community.

Currently, the Animal Resources Branch has three main objectives:

(1) to support the primate centers program,

(2) to develop a national effort to provide the types, quantities and quality of any species of animal needed for biomedical research,

(3) to determine optimum conditions for laboratory animal care, including their safety and medical treatment.

General Research Support

In 1959, as part of an appraisal of the impact of its grants program on recipient institutions, the National Institutes of Health undertook an intensive short-term study of 20 medical schools. All reported expansion in research activities over the past few years. They variously labeled this expansion as "distinctly advantageous", "contributing to widespread advancement of scientific knowledge", "enhancing the quality of education", "elevating the stature of their faculties" and "providing new strength to schools." None would retrench. Nevertheless, most schools identified a number of problems resulting from funds provided in the form of restricted

gifts and grants, particularly those from Federal agencies.

Current Program

To provide better support balance, a program of grants for general research support was instituted following passage of Public Law 86-798. These are distributed on the basis of professional evaluations of the unique capabilities and needs of the various institutions. It was decided such grants would not be made to finance specific projects but would be for use by grantee institutions to provide added strength to their research and research training programs in ways the institutions might judge to be most effective -- subject, of course, to general guidelines and policies affecting all PHS grants.

First awards under the new program were made in January 1962. By July 1 a total of $20 million had gone to 86 medical schools, 49 dental schools, 12 schools of public health and 6 schools of osteopathy. For Fiscal Year 1963, $30 million was made available and the General Research Support program now permits (upon the satisfaction of certain criteria) the extension of support to schools of pharmacy, nursing, and veterinary medicine and to research institutes, centers, certain laboratories and other nonprofit organizations heavily engaged in health-related research.

General support awards are made according to formula and represent a percentage of the amount of Federal research project grants and contracts awarded to institutions, plus a somewhat larger percentage based on an institution's available research funds received from non-Federal sources.

Program Achievement

That general support funds have helped institutions develop the better balanced research and research training programs originally envisioned, is attested by information obtained through visits to schools and through other informal channels.

One school, for example, established and staffed a new experimental endocrinology laboratory. Within the next year or so, salaries paid from the grant will be picked up on the university budget, thus releasing General Research Support Grants funds for the development of other research activities. This school also provided and staffed a new animal surgery for research, established an instrument development shop for the research support of several basic science departments, and undertook a pilot study on the breeding of animals for research. The same award also provided support for several students beginning their research training at the post-sophomore level.

Another school appointed three top-level research professors in 1962 and engaged a fourth to join the staff in 1963. Meanwhile, the research potential of several faculty members was increased by putting them on a twelve months' salary instead of the usual nine.

A third institution established three new divisions of wholly independent research activities -- one for neurophysiology, another for molecular biology in the Department of Biochemistry, and a third for genetics in the Department of Microbiology. The same grant also provided basic salaries for a number of professionals and paid the cost of some badly needed new equipment.

Division Potential

The unifying thought knitting together all five programs, is the overall Division objective which seeks to provide for the massive specialized research facilities and resources of a health-related nature needed by an institution or a group of institutions and which serve markedly to increase research capability and productivity in the recipient institution or region. Coordinated, sustained support will be provided to key institutions and programs, giving their directors greater freedom in the exploration of all approaches to new biomedical knowledge, regardless of category or discipline. Such support also gives them a capability to do pioneering work in emergent fields of research as well as those that are well established.

It is possible, therefore, for a medical school or other institution already heavily engaged in health-related research, to plan for construction of a new research wing, expand its research staff, obtain service from a computer resource, increase its access to needed laboratory animals, establish a General Clinical Research Center, and obtain an award for health-related general research support--all in a coordinated fashion--by presenting its plans to a single NIH Division. All of its needs can be considered as a "package" and total aid matched with institutional progress and intellectual capacity.

Program Planning and Analysis

In the Office of the Chief, DRFR, program analysis is continuous, not only to define program objectives, to aid in the establishment of

priorities, and to analyze opportunities, but to measure total achievement and plan subsequent courses of action. Frequent feedback is sent to and received from the Office of the Director of NIH relating to regional and national program needs and aims. One might characterize such effort as a "commitment to excellence".

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DIVISION OF BIOLOGICS STANDARDS

Function and Responsibilities

The primary function of the Division of Biologics Standards is the administration of provisions of the Public Health Service Act that pertain to the safety, purity, and potency of biological products for human use. These include the vaccines, antitoxins, therapeutic serums, and human blood and its derivatives. They are, for the most part, developed from pathogenic or potentially pathogenic microorganisms, thus their preparation requires careful control in order to minimize safety hazards which might occur in the course of processing, and to ensure final products of satisfactory potency. Accuracy is essential in every step, for the end product is the preservation of human life.

Early History

The Federal Government's responsibility for the control of biological products began on July 1, 1902, when the Congress passed an Act to regulate the sale in interstate commerce of all viruses, serums, toxins, and analogous products applicable to the prevention and cure of human diseases. The statute, now a part of the Public Health Service Act, is basically the same as in 1902. At that time, the technical responsibilities of the biologics program were assigned to the National Institutes of Health, then known as the Hygienic Laboratory. In 1937, the Laboratory of Biologics Control was created within the then National Institute of Health, and in 1948 it was made part of the National Microbiological Institute.

In June 1955, authority was granted the Surgeon General by the Secretary of Health, Education, and Welfare to expand the biologics control function of the Public Health Service to the status of a separate division within the National Institutes of Health--the Division of Biologics Standards.

Implementation of Function

The control of biological products is based on a system of licensure. This system includes the issuance by the Secretary, DHEW, of both establishment licenses and product licenses, following determination by the Division that the prescribed standards for safety, purity, and potency have been met. These standards are set forth in regulations which are continually reviewed by Division scientists for adequacy, and revised as scientific knowledge advances.

The large-scale support which has been given the medical research in recent years is reflected in the development of improved methods of immunization and new therapeutic measures. The increasing public interest in these discoveries, has, in turn, given competitive stimulus to hasten the development of new products. Thus, the time interval between research and product availability has been materially reduced. The Division, charged with the responsibility to develop standards for these products has necessarily expanded its own research, testing, and control efforts to obviate delay in determining whether such products meet licensing requirements.

Thus, the research programs of the Division's six laboratories--Control Activities, Bacterial Products, Biophysics and Biochemistry, Blood and Blood Products, Viral Immunology, and Virology and Rickettsiology--include a diversity of projects, many of immediate practical urgency, and all having direct relation to the prime responsibility of the Division. The scope, direction, and intensity of these programs are dictated by the need to provide essential information for the development of requirements and regulations for new biological products, as well as for the continuous improvement of tests to ensure the safety, purity, and potency of all such products.

Control Activities

The Laboratory of Control Activities, supported by sections on control tests, pyrogens, and reference standards, determines the eligibility of establishments and of biological products for license. This determination is made on the basis of the integrity of management and technical personnel, the physical facilities for manufacturing and testing of products, the scientific and professional qualifications of personnel, and the evidence developed by manufacturers and the Division of continued safety, purity, and potency of products for which an application for license is being evaluated. License applications are reviewed individually when required by an *ad hoc* committee consisting of appropriate members of the staff of the Division.

Once a product is licensed, continuing surveillance is maintained through periodic inspection of the manufacturer's facilities and production methods, review of records of production and testing, and testing in the Division's laboratories of representative samples of the products. Over 7,000 control tests were carried out during 1962 to verify the safety, potency, and purity of licensed biological products. The results of these tests served as a basis for the release or rejection of the more than 5,000 lots of products submitted to the Division by manufacturers during this period. The testing procedures include a variety of tests, ranging from relatively simple sterility tests to complex and costly potency determinations and safety tests.

To assure that every lot of a product is of consistently acceptable and uniform potency, standard physical reference preparations are developed by the Division. Seventy-five such preparations are now maintained and approximately 6,000 vials are distributed annually to research and control laboratories of licensed manufacturers, health departments, and universities in this country and abroad.

Biophysics and Biochemistry

Basic research on the physical and chemical factors that determine the biological properties of viruses, bacteria, and rickettsia, as well as their host cells, is an integral part of the Division's research program. The Laboratory of Biophysics and Biochemistry is engaged in the study of biophysical methods of analysis, including ultracentrifugation and electron microscopy, supplemented by specialized techniques for concentrating and purifying the microorganisms for study. An immediate objective of the Laboratory is the development of methods for rapid characterization of newly identified viruses.

Other biophysical studies in progress include an investigation of the mechanism of thermal inactivation of viruses, determination of the relative susceptibility of animal viruses to photodynamic inactivation, development of methods for differential inactivation of simian viruses in suspensions of live attenuated polioviruses, and the study of the effects of various physical and chemical stresses upon metabolism of tissue culture cells.

The study of photochemical processes affecting survival of viruses has led to the development of a photosensitization technique for differentiating between parent and progeny virus in cell cultures. This has made it possible to detect multiplication of poliovirus in non-primate cells that were previously thought to be refractory to infection. This finding has some bearing on the developing concepts of the relationship between viruses and their animal hosts.

Basic information obtained in studies of this type aids in understanding the problems encountered in production, testing, and control of biological products of microbial origin.

Bacterial Products

The Laboratory of Bacterial Products' research is related to the continued quality and improvement of bacteriological products and to the development of methods for the control of new ones. These products include cholera, pertussis, typhoid, and BCG vaccines; diphtheria and tetanus toxoids; antibacterial antitoxic serums; and allergenic products.

Cholera vaccine, one of the first immunizing agents to be introduced in this country, was licensed in 1910. The disease is still prevalent in some parts of the world, and with the present-day speed of international travel could constitute a real threat if introduced into receptive areas. The Division has taken an active part in the World Health Organization's program for the development of international recommendations for cholera vaccine which would facilitate the exchange of vaccines between countries in times of emergency.

Experimental work is directed toward the development of quantitative potency tests for laboratory evaluation of cholera vaccine and the establishment of a U. S. standard vaccine. This research is coordinated with the SEATO Cholera Research Project and with international efforts to determine the relation between laboratory evaluated potency and human protection.

For many years, pertussis, or whooping cough, ranked among the most fatal communicable diseases of childhood. Although pertussis vaccine was licensed in 1914, it was in and out of favor for many years. As recently as 1940, the death rate from pertussis in children under one year of age was 2.6 times that of measles, scarlet fever, diphtheria, poliomyelitis, and meningococcus infections combined. The development of a laboratory test, initiated at that time by Division scientists and others, led to the adoption of a U. S. standard of potency for pertussis vaccine. Within 10 years, there was a tenfold drop in death rate and a 70 percent drop in case rate. In 1958, the World Health Organization established an international standard pertussis vaccine with an assigned unit of potency based on the U. S. unit.

A skin test for susceptibility to diphtheria was introduced in 1913 by Bela Schick, an Austrian pediatrician. Today, most children are given primary immunization with diphtheria toxoid and are therefore Schick-negative. Among adults, however, there is an increased susceptibility to diphtheria. It has been found that a small dose of diphtheria toxoid is capable of inducing satisfactory levels of antitoxin in a large percentage of these young adults with no untoward reactions. The Laboratory's scientists are attempting to establish an improved method for evaluating the diphtheria toxin for the Schick test and to develop a dried U. S. standard for the Schick toxin.

With the increasing availability of immunizing antigens there has been a trend in recent years toward combining several antigens in a single product. Diphtheria and tetanus toxoids combined with pertussis vaccine have been in use a number of years. In 1959, a fourth antigen, poliomyelitis vaccine, was added, thus making possible the simultaneous immunization against four childhood diseases. Studies are being carried out on the effect of combined antigens on the antigenicity of the individual antigen.

Blood and Blood Products

The various fields of interest in the Laboratory of Blood and Blood Products have as their goal the improvement of testing procedures used for the control of biological products derived from blood--these procedures being designed insofar as possible to insure the safety, purity, and potency of these products. The projects cover all phases of blood collection, processing, shipment, and storage. Investigations encompass not only improvements for existing control procedures but also are directed toward the perfection of new tests for existing products as well as for new products.

Studies are presently being carried out on the various components of the coagulation system. Some of the new products under development have immunological or biological activities for which there are no established test criteria. Research on some of the fundamental characteristics of these proteins is being done to gain information on which useful control tests might be based. Further improvements have been made in the method of preparation of a plasminogen-free fibrinogen; an important accomplishment since it brings one step closer the goal of control tests for the complex coagulation systems that are independent of the reagents used.

Other research interests of this Laboratory include studies of freezing, storage at various low temperatures, thawing and/or drying of the many elements of whole blood and protein fractions of plasma. Specific investigations within this broad field are undertaken to obtain data on which to base dating period and stability of products.

For many years, the Laboratory has maintained an active research interest in the effect on the properties of whole plasma and the individual plasma proteins of time, light, container material, temperature fluctuations, and other factors. Normal serum albumin was placed on such a long-term study eight years ago. The subtle changes which occur are taken into account in establishing a dating period schedule for this product.

Immunological studies related to the identification and quantitation of antigens on red blood cells and other formed elements and of the antibodies which occur in blood are being carried out by the Laboratory. Many control tests still have an empirical basis. An ultimate goal of these immunological investigations is control tests which result in realistic quantitative expressions of identified antibodies or antigens.

Viral Vaccines

Influenza Vaccine

During the past year a number of variants of the influenza virus strains have appeared in this country. In cooperation with other interested laboratories, the Division has paid close attention to these variants with a view to the possible selection of an additional virus strain for inclusion in the vaccine now in use. The last change was in 1957 when the Asian strain of influenza due to an A2 type of virus spread throughout the world. By December 1962, it appeared that the incorporation of new strains in the vaccine would again be called for and appropriate studies were initiated by the Division in cooperation with manufacturers and specialists in this field.

The results obtained in the Laboratory of Virology and Rickettsiology indicated a shift in antigenic composition in some of the 1961-62 Asian strains had occurred. Antigenic analysis of influenza B strains recovered in the winter of 1961-62 in outbreaks of influenza in the United States and Canada indicated a clear, but relatively small, antigenic difference between the recent strains and the older strains contained in the current vaccine.

As a result, it has been recommended that one of the new A2 variant strains and one of the recent B strains be incorporated into the vaccine manufactured for the 1963-64 influenza season.

Live Poliovirus Vaccine

Although a continuing interest is maintained in areas of research which are well established, such as smallpox and the rickettsial diseases, the newly developed biological products place the heaviest demands on the Division.

Complex problems have emerged during the past several years in the process of evaluating the results of wide-spread use of the live poliovirus vaccine. While these were largely epidemiological, the extent of related laboratory studies carried out in the Division's laboratories indicates the scope of research on control methodology for such candidate products. The major portion of this work is the responsibility of the Division's Laboratory of Viral Immunology.

Types 1 and 2 of the Sabin strains of the live, oral poliovirus vaccine were licensed during the fall of 1961; Type 3 was licensed six months later. The delay in licensing the Type 3 strain--genetically the most labile of the three--was caused by difficulties encountered under manufacturing conditions in the production of five consecutive lots of vaccine that would meet the requirements for a low degree of neurovirulence in monkeys, as well as specific characterizations required in tissue culture tests.

The monkey neurovirulence tests required for all three types of live poliovirus vaccine involved extensive laboratory study. Approximately 150 neurovirulence tests in 4,000 monkeys were made on vaccine samples submitted by the manufacturers. This testing provided a wealth of information and experience that has been invaluable in judging the validity of subsequent tests on individual lots of vaccine.

Measles Vaccines

Two significant scientific advances in the field of virology laid the foundation for a rational approach to immunization against measles: 1) In 1954, Drs. Enders and Peebles isolated measles virus in tissue culture and subsequently adapted it to different tissue culture systems, including the chick embryo. 2) Enders and co-workers demonstrated that one of the strains with which they were working--the so-called Edmonston strain--after a series of passages through various tissue culture preparations, ending with a series in chick embryo tissue culture, produced no apparent disease when inoculated into monkeys and only mild disease, associated with significant development of measles antibodies, in susceptible children. Thus the tools were provided whereby the measles virus could be readily isolated, its infectivity accurately determined, and its pathogenic, immunogenic, and other biologic properties studied.

These findings established the groundwork for future studies directed toward the development of vaccine composed of either attenuated or inactivated measles virus. Much further work was necessary, however, to determine whether the development of such vaccines was feasible. Satisfactory methods for cultivating the virus on a large scale were essential. There was the need to evaluate the safety, effectiveness, and stability of a vaccine so produced. Finally, it had to be determined if the vaccine-induced antibodies would protect against exposure to natural infection.

Anticipating that development leading to useful vaccines might be relatively rapid, the Division arranged for a number of conferences with interested investigators and potential producers to discuss the problems of evaluating such vaccines. These conferences fostered an interest and an awareness of the problems among those capable of significant contributions once vaccines became available for evaluation.

In April 1958, some 50 scientists concerned with basic experimental virology and large-scale production of vaccines in general, met at the

National Institutes of Health to consider the potential developmental and clinical problems inherent in the production and control of an immunizing agent against measles.

In November 1960, the Division arranged another conference to assess and correlate the progress made during the preceding 18 months. Clinical data presented by investigative groups using the live virus vaccine made from the Enders Edmonston strain gave evidence of its capacity to elicit satisfactory protection against natural measles as well as specific antibodies among the vaccinees. The Enders vaccine was shown by three groups of investigators to give complete protection in children exposed to natural virulent measles virus, while the unvaccinated persons showed the expected high incidence of the disease. Evidence of the satisfactory persistence of antibody titer for at least 18 months was also presented. The Enders vaccine, in many cases, caused some mild clinical reaction--principally fever. While this was tolerable, it was considered desirable to have a preparation free of such side effects. When administered concurrently with gamma globulin, such reactions were markedly reduced.

In November 1961, an International Conference on Measles Immunization was held at the National Institutes of Health under the joint auspices of the Division of Biologics Standards, the National Institute of Allergy and Infectious Diseases, and the University of Colorado. Investigators from 22 countries presented a variety of reports which, in effect, reviewed and summarized the epidemiology of measles in various areas of the world, the available clinical and experimental data concerning the use of vaccine, as well as consideration of problems encountered since the review at the 1960 Conference and those likely to be encountered in the future. The indications were clear that prophylaxis against measles by vaccination could be accomplished, and that one or more vaccines for measles prevention would probably soon be available once the problems of producing vaccines on a large scale suitable for general distribution and use had been solved.

The development of regulations for measles vaccines called for an extensive array of controls, since three products are involved--live measles vaccine, inactivated measles vaccine, and standard gamma globulin for use with the live vaccine.

The regulations cover the characteristics of the measles virus strains to be used in the vaccine; the exclusion of adventitious agents from the virus fluid used in manufacture; the employment of a variety of animal and tissue culture test methods; the demonstration of satisfactory clinical use of the vaccine, including clinical effectiveness; and the stability of the live virus vaccine strains in terms of capacity to revert to significant virulence in man.

In March, 1963, licenses for the manufacture of both the killed and live virus measles vaccines were granted, making it possible to eliminate another infectious disease of childhood.

The Division's Laboratory of Virology and Rickettsiology has added materially to knowledge regarding the use of live attenuated measles virus vaccine through its studies in West Africa. These, undertaken as a collaborative venture by the Division, the Ministry of Health of Upper Volta, and the Agency for International Development, have demonstrated that Voltan children respond in the same manner as American children to the live vaccine, whether given alone or in combination with gamma globulin. Because measles is one of the serious diseases of Upper Volta, with mortality rates running as high as 50% at times, and because the Volta health officers and the people do not object to the mild illness which is common when attenuated virus is given without gamma globulin, plans were made for a large-scale measles vaccination program using attenuated vaccine alone in all susceptible children under three years of age.

This represents the first attempt to eradicate measles from a nation. The original plan called for the inoculation of 100,000 children. Before the plan became operative in early November 1962, this figure was raised to 300,000 on the basis of a new census of the population. At the termination of the study in February 1963, over half a million children had been vaccinated.

The vaccine was administered parenterally by jet injection by Voltan teams traveling through the entire country, district by district. Each team consisted of three Voltans, employed by the Ministry of Health, equipped with a jeep, two jet guns, an electric generator for operating the guns, and a portable refrigerator for transportation of the vaccine. Each of the eight teams were trained, advised, and assisted by the three-member team from the Division.

The ultimate success of the mass immunization program will be judged by the reduction in measles during this year's annual epidemic; however, it is already apparent that the experience has provided worthwhile information on how measles immunization can be accomplished in a developing nation.

Adventitious Agents

The Division has also been concerned with adequate procedures for examining vaccine lots for the presence of adventitious agents, such as SV-40--one of the 40-odd simian viruses encountered during the preparation of monkey kidney cell culture vaccines. Since, with few exceptions, the role of these viruses in the production of human disease is unknown, the Division requires their exclusion from all commercial vaccines. Identification and elimination of these occult viruses constitutes a vexing problem for the manufacturers as well. Since they cannot be detected by routine tests normally employed in vaccine production and control, elaborate test systems must be devised.

SV-40, first identified by Drs. Sweet and Hillemen in 1960, was found in 1961 to be present in residual amounts in certain lots of killed polio vaccine, as well as in adenovirus vaccine. Although it is not known to produce disease in man, nor does its presence in the vaccines prevent the development of immunity against the disease in vaccinated persons, it has been found to produce cancer in newborn hamsters and therefore, has become emotionally linked with cancer in human beings, although no such relationship has been demonstrated.

SV-40 is indigenous in wild rhesus monkeys in India, and the virus is a common infection of these monkeys by the time they reach research and biological laboratories in this country. The virus has not been found to produce recognizable clinical disease in rhesus or other monkeys. Moreover, although it grows in tissue culture prepared from rhesus kidney cells, it does not produce recognizable cytopathogenic changes in the cells. However, the virus does cause definite changes--the vacuolating effect which gives it its name--in kidney culture cells obtained from African (cercopithecus) monkeys. It was this property which led to its discovery. Although SV-40 was not recognized until 1960, serological eivdence from stored monkey sera indicates that as early as 1953 rhesus monkeys used in laboratory experiments were infected with this virus.

Since May 1961, all lots of poliomyelitis and adenovirus vaccines released have been tested for SV-40, and only those free of this agent have been cleared by the Division for commercial use. Since killed poliomyelitis vaccine can be manufactured free of SV-40, the availability of adequate quantities of vaccine was not seriously curtailed. However, few manufacturers were in a position to begin immediate testing for this virus, and a testing program was carried out by the Laboratory of Viral Immunology to assure adequate supplies of poliomyelitis vaccine following the May 1961 decision.

In order to determine whether conditions of trapping, handling, and shipping were important factors in obtaining virus-free monkeys, Division investigators went to India to supervise the handling of rhesus monkeys from the moment of capture to their arrival at NIH laboratories. Their findings confirmed that SV-40 is an enzootic infection indigenous in the rhesus monkey.

The discovery that SV-40 was the oncogenic agent responsible for the induction of tumors in hamsters injected when newborn with extracts of rhesus monkey kidney cell cultures was made by a Division scientist, as was the discovery that SV-40 is susceptible to photodynamic inactivation.

The production and testing problems posed by adventitious agents indicates a need for tissue culture cell systems free of contaminating viruses which could be used with full confidence in vaccine production and testing. An example of such a system is the continuous cell line derived from cercopithecus monkey tissue which has been developed in the Division's laboratories.

Such a cell line, the Biologics Standards-Cercopithecus-1 (BS-C-1) cell line, was initiated in March, 1960, from kidney tissue of _Cercopithecus_ _aethiops_ by the _Laboratory of Virology and Rickettsiology_. It is now in its 125th passage and is considered to be an established cell line. Cultures have been sent to the Cell Bank Committee (sponsored by NCI) for characterization and subsequent storage at the American Type Culture Collection. The BS-C-1 line is unique in that this is the only reported continuous culture whose chromosomal pattern and virus susceptibility have been studied in concert since early passage levels. Findings indicate that while the chromosomal pattern of the cells changed from diploid (30th passage) to subdiploid (at 41st passage) to heteroploid (111th passage), the cells have not changed their sensitivity to SV-40. Moreover, at the 108th passage they were still sensitive to attenuated measles virus. Further evidence of their stability with regard to virus proliferation was noted in studies with influenza A and B and adenoviruses 3, 4, and 7. The BS-C-1 line was refractory to these agents at low passage and still failed to support their growth at the 95th passage level. In addition to those viruses already reported to multiply in BS-C-1 cells--SV-40, measles, and attenuated polioviruses 1, 2, and 3--it has been shown that this line will support growth of Rift Valley fever virus, Rous Sarcoma virus, O'Malley's A-1 agent, Coxsackie A9, and simian viruses 1, 4, and 5 but not SV-2. Preliminary data suggest that the line may be useful in basic studies with epidemic typhus rickettsiae. The cell line has come into general use in the scientific world; 46 research and industrial laboratories in North America, Europe, Asia and Australia have been supplied on request with seed cultures.

Budget and Organization

Funds available for the Division of Biologics Standards during fiscal year 1963 totaled $3,947,000. The total personnel as of December 31, 1962 was 219: 52 professional, 129 technical, 27 clerical and administrative.

REVIEW AND APPROVAL ACTIVITIES

DIVISION OF RESEARCH GRANTS

The research grants program of the Public Health Service had its origin in a small group of medical research contracts that were transferred from the wartime Office of Scientific Research and Development late in 1945. A unit was needed within the PHS to administer these grants, and the Division of Research Grants was established at the National Institutes of Health in January 1946.

Since that first year--when the staff comprised fewer than 30 people--DRG has expanded its organization to meet responsibilities growing in magnitude and complexity. As of December 31, 1962, there were 535 scientific, administrative, and clerical personnel. A major portion of the PHS research and training grant program is now coordinated and centrally administered within the Division of Research Grants at the National Institutes of Health.

In addition to its original mission--the processing and scientific or technical review of grant applications--other functions of DRG now include initiation of surveys to determine the status or need of research in the various disciplines of importance to health and medicine; provision of fiscal review and financial management of the PHS extramural program; documentation of the scientific areas covered by PHS research grants; coordinating the formulation of policies and procedures governing the entire PHS extramural programs; providing statistical and analytical services for the PHS extramural programs; and a variety of general and technical information services.

Brief functional statements for the principal types of research and training support with which the Division is concerned follow:

I. Research Grants - Research grants are made to universities, hospitals, laboratories, and other public or private nonprofit institutions and to individuals for support of research in health, medicine, and allied fields, including experiments, or demonstrations relating to the development, utilization, and coordination of hospital services, facilities, and resources. The major objectives of the research grant program are (a) to expand medical and biological activities in research institutions throughout the country, (b) to stimulate new investigations in fields needing exploration, and (c) to provide as a by-product on-the-job experience for scientific personnel in connection with the research being conducted. These funds provide for salaries, equipment, supplies, travel, and other expenses such as reprints, hospitalization, renovation and alteration of existing facilities. Three types of research grants are available: (1) Project Grants - a project grant is awarded to an institution in support of a well-defined research proposal. It may be limited to a discrete project of a single investigator or it may provide funds for support of a broad program which integrates the research interests of several investigators. (2) Clinical Center Grants - Clinical research center grants are made to institutions solely for the support of physical resources (excluding new construction) and services required in common by a number of investigators. Clinical research centers are typically large and complex and involve a physical resource to be used as the site for research. (3) Special Resource Grants - Special resource grants are designed to

support specialized or unusual services required for research in medical and related sciences, including instrument and electronic development, computing and data processing, and bio-engineering.

II. Research Fellowships - Three types of fellowships are available for research training in the health sciences: (a) Predoctoral Fellowship, awarded to qualified persons who hold a Bachelor's degree or equivalent training. Fellows are expected to carry on studies oriented toward graduate training in fields related to the health sciences. Stipends: $1,800, $2,000, and $2,200. (b) Postdoctoral Fellowship, awarded to qualified persons holding a doctoral degree. Stipends: $5,000, $5,500, and $6,000. (c) Special Fellowship, awarded directly to qualified individuals to provide advanced or special training for research, including clinical investigation. Stipend is determined on an individual basis.

III. Research Career Program - Awards are available to institutions in the United States on behalf of qualified candidates to provide increased numbers of stable career opportunities for scientists of superior potential and capability in the sciences related to health. Awards are intended to provide individuals with some measure of assured support reasonably early in their careers. Awards are made in 5-year increments. Sponsoring institutions should propose salary levels not to exceed $25,000 based on candidate's training, experience and accomplishments, and in keeping with the institution's salary scale. Two groups are available: (a) Development Awards: These awards are for young investigators who desire experience and further training in a productive research environment as well as for scientists undertaking

independent research who need further experience to qualify for senior positions. (b) Career Awards: Awards in this group are intended to finance additional stable positions for experienced investigators who are continuing to develop in productive careers of independent research and teaching. Awards are made on the basis of nationwide competition, and the research standards expected of candidates are high.

IV. Undergraduate Training Grants - Undergraduate training grants are awarded to medical schools, dental schools, schools of public health, schools of nursing, and schools of osteopathy to assist in developing expanded and better integrated undergraduate instruction in the special fields concerned. It is the responsibility of the institution to determine the most appropriate use of the funds.

V. Graduate Training Grants - Graduate training grants are awarded to public and private nonprofit institutions to provide for special training for researchers, teachers, and prospective practitioners interested in public service. These funds may be used to provide salaries for faculty, staff, and trainee, along with necessary supplies and materials, and to improve facilities.

The official point of receipt for most research and training grant applications is the Division of Research Grants. The Division is responsible for the assignment of research and training grant applications to Institutes or Divisions and for the entire initial review process for research grants and fellowships. The assignment and initial review functions are conducted by two branches of the Division of Research Grants: the Research Grants Review Branch and the Career Development Review Branch.

The organizational relationships of these two branches are seen in Chart I.

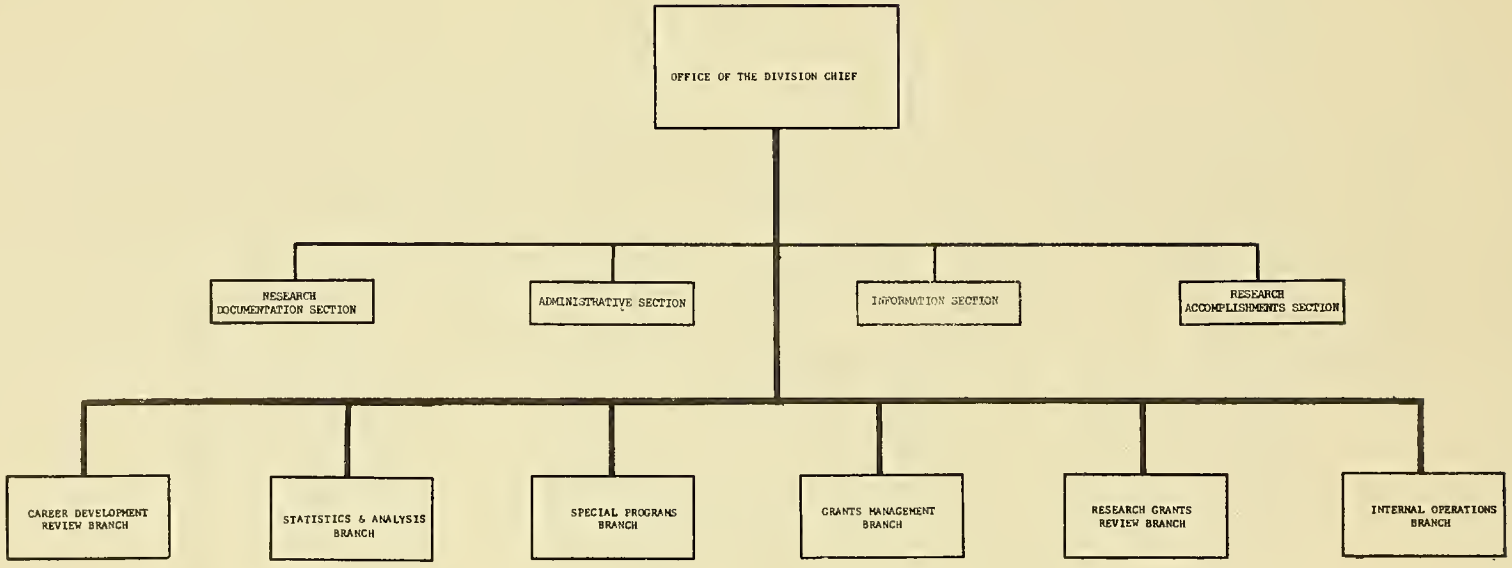
Research Grants

The Division's Research Grants Review Branch receives all applications for research grants and assigns them, on the basis of subject, to an appropriate Study Section or Committee within DRG for initial review and to an Institute or Division for final review and financial support if approved. The Branch includes 46 advisory panels (called study sections) each of which consists of distinguished scientists who represent various disciplines of health research, including related research in the biological, behavioral and physical sciences. The Branch has responsibility for proposing study section members who are recognized experts in their respective fields and who will add needed competence in the areas covered in their sections. The Branch also formulates procedures for grant review and serves as an information and coordination center for applications pending review.

At the outset of the research grant program, 21 study sections were established. As appropriations to the NIH for its extramural programs increased and additional programs were initiated in the Bureau of State Services, the volume of applications has grown steadily and the workload has become correspondingly heavier. To assure continuance of the highest possible standards of review, several steps have been taken. Additional study sections were created, existing ones were subdivided, or new members were added to strengthen them. The present complex of study sections covers the basic sciences, major disease areas, environmental health,

CHART I

ORGANIZATION CHART OF DIVISION OF RESEARCH GRANTS


OFFICE OF THE DIVISION CHIEF
RESEARCH DOCUMENTATION SECTION
ADMINISTRATIVE SECTION
INFORMATION SECTION
RESEARCH ACCOMPLISHMENTS SECTION
CAREER DEVELOPMENT REVIEW BRANCH
STATISTICS & ANALYSIS BRANCH
SPECIAL PROGRAMS BRANCH
GRANTS MANAGEMENT BRANCH
RESEARCH GRANTS REVIEW BRANCH
INTERNAL OPERATIONS BRANCH

and community health. The DRG appoints one of the members as chairman, and provides a scientist-administrator as executive secretary and additional staff as needed.

Research Training

The Career Development Review Branch is responsible for (1) examination of applications for predoctoral, postdoctoral and special fellowships, graduate training grants, and research career program awards for acceptability and assignment to the appropriate Institute or Division; (2) scientific review and evaluation of the three types of fellowship applications in a manner similar to the study section review of research grant applications; (3) coordinating the development and implementation of uniform policies and procedures for central management of training award programs, (4) periodic analyses of current professional activities of former fellows and trainees and other studies important to health research training, and (5) capture and retrieval of core data on all training award applications.

Other Functions

In addition to its review and approval responsibilities, the Division serves as the Public Health Service's coordinating unit for management of research and training grants, and as a central source of information for personnel in over 1,200 grantee institutions. The Division negotiates agreements with grantee institutions to establish fund control systems, and makes periodic analyses in grantee institutions of such matters as hospitalization costs, salary policies, and invention reports. In the development of grants policies and procedures, the staff studies

problems inherent in new support programs before these programs are established, accumulates case histories and precedents, and provides the Institutes and Divisions with standards and guidelines for reviewing grant budgets and related documents.

Another service performed by the Division is the collection of statistical data on the more than 20,000 active grants and awards of all types comprising the Service's extramural research program. The Division collects data from applications and other sources; codes the data on magnetic tape for the electronic computer, and produces compilations and analyses to accommodate the requirements for program management. The Division produces 50 to 60 periodic statistical reports and compilations each year, including the annual listings of PHS grants and awards by State and Institution.

More recently, the Division has been providing important additional tools for review groups in assisting in the evaluation of applications for support. Reports of accomplishments resulting from PHS-supported programs, particularly the dividends from basic research efforts,have aided the evaluation of proposed work as well as the determination of areas that need to be explored. The Research Grants Index, published annually by the DRG gives, for the first time, a subject matter arrangement of all PHS research grants, with identification of the investigators who are working in specific areas.

Reviewing Groups

In general, applications to the NIH for research support are reviewed from two viewpoints: (1) scientific merit - an initial review,

which emphasizes the scientific merit of the proposal, the ability of the applicant, adequacy of the environment and resources, and soundness of the financial estimate, and (2) program significance - this is the final review, which, in light of the assessment of merit, reflects policy, relevance of the proposal to the overall program, and other broad considerations.

If the applications are for support of research, as distinguished from research training, for example, the initial review is carried out usually by study sections, but at times by other committees. If the applications concern training, then the initial review is provided by either training committees, fellowship review panels, or research career award committees.

The final review is conducted either by national advisory councils or national advisory committees in the case of research grant or training grant applications, or, in the case of fellowships, by fellowship specialty boards. These groups then make appropriate recommendations to the Surgeon General of the Public Health Service for final action.

Initial Reviewing Groups

Study Sections - The study sections form the largest class of initial reviewing groups, since they review applications for research grants, by far the largest category of support. Study sections average fifteen members, most of whom are university scientists, and all of whom are experts in their fields. The study sections are organized according to biomedical disciplines, such as biochemistry or surgery, or health problem areas, such as metabolic diseases, or accident prevention. They function

administratively as part of DRG, and have responsibility for transmitting the panel's findings and recommendations to the appropriate Institute or Division. A second function of study sections is the assessment of research needs in their respective fields.

Program-project, center, and special resource review committees - These committees are similar to study sections, but, since they are concerned with the larger grants and must give even more consideration to the administrative and fiscal aspects of applications in relation to the scientific aspects, their membership includes such persons as college deans, hospital administrators, and cost accountants, as well as scientific experts.

Training committees - Applications for training grants are reviewed by training committees, which are organized either according to disciplines or more general fields of interest, and administratively placed under the various institutes and divisions of the PHS. In composition they are similar to study sections. Training committees, like study sections, have executive secretaries from PHS staff who provide liaison with the councils. Some of the training committees review applications for research career awards as well as for training grants.

Fellowship review panels - Predoctoral, postdoctoral, and special fellowship applications are reviewed by a Central Qualifications Board, consisting of twelve fellowship review panels, and functioning administratively within the DRG. Fellowship applications do not require council review, their final review being provided by fellowship specialty boards within the institutes and divisions. Members of these groups are drawn from much the same sources as are members of study sections and training

committees. The Division has administrative responsibility for the following public and advisory groups:

STUDY SECTIONS

Accident Prevention

Allergy and Immunology

Bacteriology and Mycology

Behavioral Sciences

Biochemistry

Biophysics and Biophysical Chemistry

Cancer Chemotherapy

Cardiovascular

Cell Biology

Communicative Sciences

Dental

Endocrinology

Environmental Sciences and Engineering

Experimental Psychology

General Medicine

Genetics

Health Services Research

Hematology

History of the Life Sciences

Human Ecology

Human Embryology and Development

Medicinal Chemistry A

Medicinal Chemistry B

Mental Health A

Mental Health B

Metabolism

Neurology A

Neurology B

Nursing Research

Nutrition

Pathology A

Pathology B

Pharmacology and Experimental Therapeutics

Physiological Chemistry

Physiology

Primate Research

Psychopharmacology

Radiation

Special

Surgery A

Surgery B

Toxicology

Tropical Medicine and Parasitology

Virology and Rickettsiology

Visual Sciences

Advisory Committee on Computers in Research

Allergy and Infectious Diseases Program-Project Committee

Arthritis and Metabolic Diseases Program-Project Committee

CENTRAL QUALIFICATIONS BOARD
FELLOWSHIPS REVIEW PANELS

Anatomy and Pathology

Behavioral Sciences

Biochemistry and Nutrition

Biophysics and Biophysical Chemistry

Cell Biology

Clinical Research

Medicinal and Organic Chemistry

Mental Health

Microbiology

Pharmacology and Endocrinology

Physiology

Psychological Sciences

FINAL REVIEWING GROUPS

There are thirteen advisory councils and committees responsible for final review of applications to the PHS. They are:

National Advisory Allergy and Infectious Diseases Council

National Advisory Arthritis and Metabolic Diseases Council

National Advisory Cancer Council

National Advisory Dental Research Council

National Advisory Heart Council

National Advisory Mental Health Council

National Advisory Neurological Diseases and Blindness Council

National Advisory General Medical Sciences Council

National Advisory Council on Health Research Facilities

National Advisory Health Council

National Advisory Research Resources Committee

Federal Hospital Council

National Advisory Child Health and Human Development Council

In general, members of these final reviewing groups are drawn from the fundamental sciences, medicine, education, or public affairs, and are appointed by the Surgeon General for four-year terms. Membership is usually twelve, half or more of the members being specialists or authorities in the relevant fields, the remainder lay members. There are also usually two or three ex-officio members representing federal agencies having an interest in health research.

All research and training grants, research facilities construction grants, and general research support grants must be favorably recommended by one of the councils, and must have the approval of the Surgeon General before payment can be made.

The councils meet three times a year to advise the Surgeon General on the merits of applications under review and to make recommendations for approval or disapproval. They also advise the Surgeon General on matters of national policy and programs in their areas.

For the formal, initial reviews, the study sections, panels, and other committees meet regularly three times a year. Much of the actual study of applications, however, is carried out in advance of these meetings by individual members who are assigned review responsibility for applications in their field of particular competence.

In evaluating the scientific merit of applications, members of initial reviewing groups consider all available information about the scientific ability of the applicant, his institution, and work by others in the field

in question. During the course of review of an application, a visit may have to be made to the site of the proposed project for interviews with the applicant, his supervisors, and his staff. No member of any advisory group may take part in reviewing applications coming from his own institution.

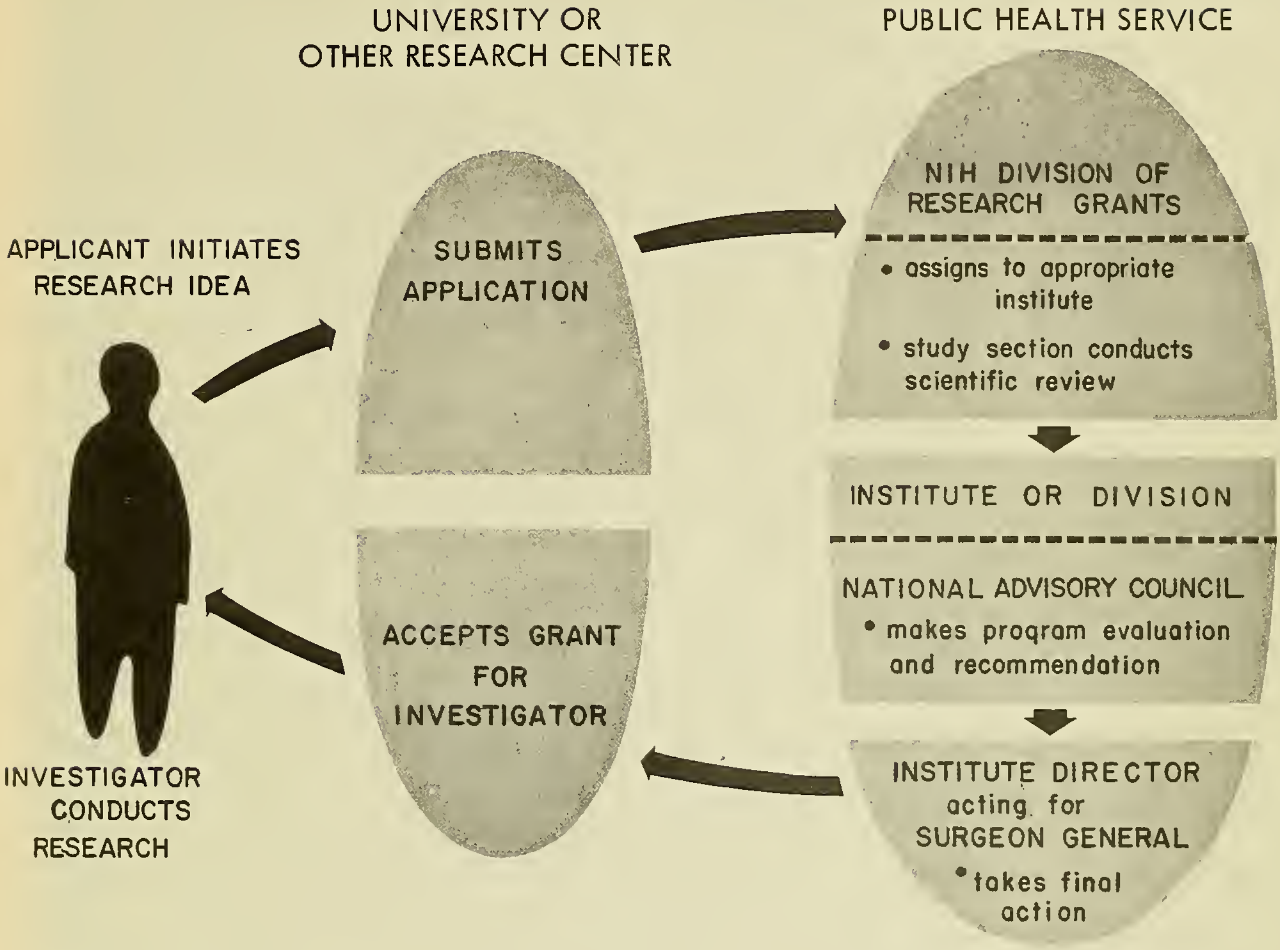
The technical reviewing groups also recommend, for each research or training grant and each fellowship application approved, a priority score reflecting the consensus of the group on the relative significance of the proposal.

While the councils in the great majority of cases concur in the recommendations of the technical groups, they may at times recommend a different action to the Surgeon General. Therefore, a favorable recommendation at either the initial or final review level does not guarantee payment of a grant. The Surgeon General's approval is further based on program consideration of the PHS and adequacy of funds in the particular field of research. No project or program can be initiated until necessary approvals are obtained, funds are obligated, and the applicant is notified by the Institute or Division that a grant is being awarded and that funds will be available at a specified date.

(Chart II)

CHART II

REVIEW OF A RESEARCH GRANT


UNIVERSITY OR OTHER RESEARCH CENTER
PUBLIC HEALTH SERVICE
APPLICANT INITIATES RESEARCH IDEA
SUBMITS APPLICATION
NIH DIVISION OF RESEARCH GRANTS
• assigns to appropriate institute
• study section conducts scientific review
INSTITUTE OR DIVISION
NATIONAL ADVISORY COUNCIL
• makes program evaluation and recommendation
INSTITUTE DIRECTOR acting for SURGEON GENERAL
• takes final action
ACCEPTS GRANT FOR INVESTIGATOR
INVESTIGATOR CONDUCTS RESEARCH

OFFICE OF INTERNATIONAL RESEARCH

Background and Legislative Authority

Growth of medical knowledge in the United States up to World War I depended to a large extent on the flow of information and knowledge from Europe. Our own medical research, which became of age between the two World Wars, was then subjected to even greater demands by the increasing recognition of the importance of medical research associated with the rising standards of living and medical care which followed World War II.

The renewed flow of skills and ideas from Europe facilitated the spectacular growth in scope and productivity of American medical research following World War II. It was during this period when the United States was coming into a position of world leadership in medical research that the basic interdependence between Europe and America for stimulation of ideas and interchange of skills came to be understood as necessary for rapid progress of medical science both nationally and internationally.

Early official U. S. recognition of the usefulness of foreign research resources and talents in throwing light on our domestic medical problems was in the 1930 Act of Congress which (in establishing the National Institute of Health) authorized fellowship arrangements for sending American scientists overseas for training and to carry on investigations in foreign localities or in collaboration with foreign scientists. The concept was greatly broadened in Section 301 of the Public Health Act of 1944 and related legislation establishing the categorical research Institutes which authorized the present grant and fellowship programs and permitted them to be conducted both in the United States and abroad.

Explicit legislative recognition of the importance of international medical research activities to progress of the health sciences in the United States came in the International Health Research Act of 1960 (PL 86-610). This Act authorized the Surgeon General of the Public Health Service to carry on "cooperative endeavors with other countries in health research and research training." In the same Act Congress recognized a permanent U. S. interest in international cooperation to further the "international status of the health sciences," an interest which had previously been manifested mainly through the various foreign aid programs. The Act authorized the President to carry out "cooperative enterprises in health research, research planning, and research training." This authority has been exercised by the National Institutes of Health under limited and specific delegations in such instances as the financial assistance provided to the World Health Organization and the Pan American Health Organization through research planning grants.

Philosophy

The National Institutes of Health have in recent years greatly increased the use of foreign scientific resources to carry forward their medical research objectives. By selecting appropriate projects among the many foreign opportunities offered abroad, the Institutes are supplementing domestic resources both in quantity and scope. Thus, our own supply of highly trained scientists in certain fields is being reinforced by grants affording partial support for outstanding foreign scientists working on projects of mutual interest and concern.

Use of foreign scientific resources and environments not only adds unusual talent and the stimulation of other ideas, but it affords a greater variety of techniques and approaches to solve problems related to causation, prevention and treatment of diseases of importance to the American people as well as those of other nations.

Studies of geographic pathology and epidemiology carried on among divergent national and ethnic groups make it possible to compare genetic and environmental factors in disease and thus may provide important clues to the causes of certain diseases which might not become evident in studies restricted to our own environment.

The international activities of the National Institutes of Health are not a separate program with its own objectives. Rather, they represent the aggregate of the foreign segments of the programs of the categorical Institutes which are directed toward advancing the health sciences in the United States, and thereby the health of the American people.

Collaboration of foreign scientists and institutions is, for the most part, readily offered because few of the health problems of the American people are unique. Most of them represent equally serious problems for other scientifically advanced countries. This mutuality of interest leads to a ready interrelationship and interdependence which is the basis for scientific cooperative efforts.

Scope of International Scientific Activities

NIH international scientific activities have grown both in scope and magnitude in recent years. Generally, these activities fall within one or more of three general types: support of research projects, support of research training, and support of research communications - that is, interchange of information and skills. The principal international activities and the funds expended for their support are listed in table I. The geographic distribution of the major programs is shown in table II.

Support of Medical Research

As indicated in table I, the principal mechanisms involved in NIH support of research overseas are research project grants to foreign investigators and international organizations, research contracts, and collaborative research project agreements financed by foreign currencies derived from sales of agricultural surpluses (Public Law 480).

Research Grants

The total number of research grants to foreign investigators and international organizations increased from 573 in fiscal year 1961 to 816 in 1962, and the amount awarded from $9,210,946 to $13,559,661. Foreign grants also increased in importance within the research grants program: from 3.4 percent in fiscal year 1961 to 4.3 percent of the total of regular research grants in fiscal year 1962. In this calculation, grants for general research support made for the purpose of enlarging and improving the research resource base are not included, because grants for this purpose are not made to foreign institutions.

The rapid growth of foreign applications for support gave rise during fiscal year 1962 to several measures designed to insure greater selectivity and scientific excellence in award of grants to foreign investigators and to control their growth. These include:

1. Application of more restrictive criteria for selection of foreign projects and limiting foreign awards to projects which scored better in scientific merit than the average for domestic awards. To be eligible for support foreign proposals have had to meet the following criteria:

   (a) The research proposed (1) is outstanding or original in concept, or (2) would utilize skills, materials, or other resources not likely to be available in the United States; and

   (b) The proposal is of such a nature that the results are likely to advance significantly the status of the health sciences in both the country of the applicant and the United States.

2. Shifting the burden of indirect costs to recipient institutions.

3. Duration and magnitude of commitments to foreign institutions was restricted by limiting commitments to 3 years except in unusual circumstances, and by subjecting requests for more than $100,000 to special scrutiny. This limitation on the size of foreign grants reinforces the existing policy which restricts general program support and resource development grants to domestic institutions.

4. A dollar ceiling limiting foreign grants to 4 percent of regular research grants (excluding the resource development type of grant) was imposed.

5. NIH scientific offices were established in Europe and Latin America and arrangements were underway for similar representation in the

Far East and south Asia, to increase NIH capacity to evaluate research proposals and to study the effect of NIH activities on medical science in these areas.

The immediate effect of these measures has been to limit foreign grants in fiscal year 1962 to $13.5 million, where under previous approval rates the total might have reached $18 million. These measures have reduced awards against new applications from about 50 to 33 percent.

Analysis of the effect of these measures as well as the influence of NIH grants on local support of medical research overseas which began in fiscal year 1962 will accelerate with the availability of new overseas scientific representation. Information from this source will assist Study Sections, Councils and Institute staffs in the appraisal of foreign proposals and help answer such questions as: Will a grant inhibit or stimulate local support of this and related research?

Efforts are continuing to assure increasing local financial participation in medical research projects supported by NIH, particularly in countries of clear economic capability. However, because these countries are the ones which are most productive in fields of medical research and of greatest interest and concern to the United States, it will always be necessary to maintain a close interrelated common research effort. Nevertheless, the possibility is being explored of eliminating from NIH support the salaries of foreign investigators working on these projects. Aside from the immediate saving, and greater feasibility of withdrawal of NIH funds after they had performed a priming function, this would have the advantage of assuring that firm control of the development of science in the country concerned rested not with NIH but with the country's own scientific leadership.

Special Foreign Currency Program

Background and Purpose

In 1961, the National Institutes of Health initiated in foreign countries a program of medical research financed by U.S.-owned foreign currencies accruing under title I of the Agricultural Trade Development and Assistance Act of 1954 (Public Law 83-480), as amended. The special foreign currency program is carried out as a direct extension of the intramural research programs of the National Institutes of Health. Programs supported and intended for support are directed principally toward the solution of disease and public health problems important to both the country concerned and the research effort of the National Institutes of Health. Selected for study have been programs in areas of disease of particular seriousness to the host country, and which show promise of contributing significantly to the body of knowledge of medical research in the United States. Research considered for support is that made possible by the unique combination of qualified investigators and special research situations in the host country. However, provision can ordinarily be made in most research projects for the training of younger scientists and supporting technical personnel which will augment local scientific manpower and contribute to the development of medical science in the host country.

Research proposed for support within the regular research grants program of the National Institutes of Health is not normally considered to be appropriate for consideration in the special foreign currency program.

Fields of Study

Research in the United States or elsewhere on certain diseases or disease agents may require further study or confirmation of findings in countries where such diseases are more prevalent. Evaluation of vaccines or therapy are mor readily accomplished under these conditions.

Projects proposed for support within ths special foreign currency program will be aimed at solving characteristic health problems of the host country. They will include problems of infectious disease, nutrition, heart disease, and cancer. Large population groups where recent developments in epidemiology can permit the delineation of population characteristics, suggesting new clues to the etiology of certain diseases, are of paramount importance.

Studies will also be continued on those diseases, such as cholera, smallpox, and malaria, which persist in certain areas of the world, offering a threat to those entering them, and which can spread to other areas. The search for new biological and botanical sources of pharmaceutical products useful in the fight against cancer and heart disease, for example, will be expanded. Methodology research to prevent introduction of these diseases must be maintained.

Some of the projects contemplated, of global concern, are in the fields of virus diseases. Because of the variation in attack rates of the same disease among certain countries, unusual opportunities for comparative studies are available.

Policies Governing the Selection of Research to be Supported

Research projects proposed for foreign currency support receive the same careful review and exacting scientific appraisal as is given research projects conducted in the dollar-supported intramural programs of the National Institutes of Health. Technical advice and scientific opinions are also obtained from competent scientists and scientific bodies within the host countries. Such groups will be used to the maximum extent possible to assist in the planning and organization of projects within each country. Close coordination with the health and medical research programs of the World Health Organization and Agency for International Development will also be maintained. No project will be supported contrary to the wishes of the host country's organization responsible for the overall planning and coordination of research.

The funds of the special foreign currency program are intended to support only additive research, and will not be used to substitute for the support which each country would normally give to its research effort. Likewise, these funds will not be used to support projects which would normally be eligible for support from dollar appropriations.

Funds were appropriated in fiscal year 1961 and fiscal year 1962 to purchase U.S.-owned excess currencies of Brazil, Burma, Egypt, India, Indonesia, Israel, Pakistan, Poland, and Yugoslavia.

Visiting Scientist Program

The visiting scientist program was established at NIH in 1950 for the purpose of strengthening the mutually productive scientific work of similar centers throughout the world with that part of the scientific community represented by NIH. Highly competent foreign scientists at all levels of seniority participate in this program. These appointments provide to the visiting scientist special facilities, resources, and consultation that may not have been available in his own country. At the same time they provide to the United States an additional source of brainpower and access to new techniques, special talents and procedures, etc. The general intent of the visiting program is to provide conditions under which the participants and the NIH staff will profit most.

From 1950 to 1955 only about 60 appointments were made. Now there is an average of 120 participants in the visiting program on duty each month. Scientists and associates represent about 10 percent of the NIH senior scientific staff. The growth since 1955 is as follows:

Fiscal Year	Number	Amount
1955	26	$164,625
1956	42	270,092
1957	76	518,256
1958	110	785,284
1959	128	1,097,118
1960	138	1,035,390
1961	149	869,194
1962	190	1,052,000

Support of Research Training

Foreign-trained scientists and foreign nationals trained in the United States are contributing very significantly to the manpower base for medical research in the United States. This input now accounts for about 20 percent of the Ph.D.'s and M.D.'s entering research. Continuation of this rate will make possible the goal of doubling of American medical research manpower by 1970. Overall, in fiscal year 1962, NIH obligated $143,800,000 for training and fellowships related to this goal. About 8 percent ($11,872,000) of the amount was involved in the training of foreign nationals in the United States and training of American scientists abroad. Description of the major international elements in the training program follows.

Fellowships and Traineeships

The international segment of the overall fellowship program operates through -

1. Awards for study and research at foreign institutions made to U.S. nationals under the same general conditions as for postdoctoral fellowships at domestic institutions. There were 243 such fellowships awarded in fiscal year 1962 with stipends and travel amounting to $1,804,786, including $63,306 in related supply grants (limited to $500 per fellow) for small equipment and materials to facilitate his research.

2. The international postdoctoral fellowship program for study by foreign scientists in the United States which is administered under special conditions. This program is described fully below.

3. Training in foreign countries, by about 10 percent of the postdoctoral research investigators awarded traineeships in specialized medical research areas and technologies. In fiscal year 1962, 36 awards were made for foreign training at a cost of $402,000.

International Postdoctoral Fellowship Program

As part of the regular Public Health Service fellowship program dating from the 1930's, awards to promising foreign scientists to prepare for careers in biomedical research have become a significant factor since 1958. Although these fellowships undoubtedly help build research capabilities in other countries, the program retains a basically domestic orientation. One purpose is to enrich postgraduate biomedical training in this country by enabling foreign investigators to share their ideas and background with American colleagues. Another is to encourage foreign scientists to participate in research bearing upon American health problems - research which is often continued and extended by the fellow upon return to his home country, thus generally enhancing opportunities for future collaborative research.

The fiscal year 1962 appropriation of $700,000 supported 92 fellows. To provide some of the resources needed in starting a medical research career and make optimal use of their U.S. training, research grants up to $2,500 per year for 3 years are available to international fellows newly returned to their home countries. During fiscal year 1962, $83,287 was awarded for an initial year's support of 16 research projects of such fellows and for continued support of 16 ongoing projects.

New national fellowship nominating committees were set up during fiscal year 1962 in Venezuela and Costa Rica, bringing the total to 41 participating countries authorized to submit 4 candidates for selection by the NIH awards panel. In fiscal year 1963, nominating committees will be formed in three or four additional countries, and all of the participating countries will be encouraged to name up to six candidates. A followup survey of foreign fellows who completed their studies 2 or more years ago is being undertaken to determine the effectiveness of this program. The study will cover such factors as relation of present work to training, his present institutional setting, and allocation of his time to research, teaching, administration, and clinical practice.

Training Grants

NIH training support is accomplished through grants to U.S. academic institutions in behalf of highly qualified scientists who supervise and conduct the training. These grants provide stipends for trainees and certain research costs related to the training. In this way NIH supports more than 10,000 domestic and foreign research trainees each year.

Under special conditions young foreign scientists may participate in this training at U. S. institutions. In fiscal year 1962 about 1,000, or 10 percent, of the research training stipends were paid to foreign nationals involving an expenditure of about $6,500,000. Participation of these young investigators from abroad furthers U. S. research objectives in several ways. They provide an immediate and productive source of manpower, since they carry out important research in the course of their training. They often bring to our research programs new skills, fresh ideas, and sometimes special techniques. Upon their return to their home countries, they may use their U. S. training in research of importance to American health problems even though their subsequent work is carried out in a foreign country and supported by that country. Lastly, many continue to collaborate with and assist their American preceptors in the research begun in the United States. Despite these benefits, NIH intends to study the mechanisms, terms, and conditions of these appointments with a veiw to directing them more selectively and specifically toward needed areas of research manpower development.

A few training grants have been made to outstanding scientists in foreign countries who are prepared to transfer some of their skill and special approach to young scientists. In fiscal year 1962, 13 such grants involving $380,000 were made in 6 countries: Brazil, Canada, Mexico, the Netherlands, Sweden, and Japan. On training grants awarded up to fiscal year 1962, a portion of these grant funds could be used for stipends to nationals of the country where the training project was located. On all new grants stipends now will be available only to U. S. citizens in training there.

International Centers for Medical Research and Training

This program represents a direct response to the objective in the International Health Research Act of 1960 (Public Law 86-610) to advance the status of U. S. health science through cooperative endeavors abroad. Five centers now have been established through collaborative agreements between American medical schools and a foreign medical research institute: the University of California with the Institute of Medical Research, Kuala Lumpur, Malaya; Tulane University with University del Valle, Cali, Colombia; Johns Hopkins University with Calcutta School of Tropical Medicine, India; Louisiana State University with University of Costa Rica, San Jose; and University of Maryland with Institute of Hygiege, Lahore, West Pakistan.

Each of the international centers consists of two operational elements: (1) a research and research training activity in the United States, including both American and foreign medical investigators, which is closely related to (2) specific research and training conducted in the overseas institution where American scientists may have the advantage of conducting research under unusual environmental, ethnic, and medical conditions not available for study at home. While oriented generally toward the need of American physicians and scientists to have the stimulus of research in foreign settings, a corollary advantage of the centers is the stimulus and experience afforded the foreign collaborating institutions to develop and expand indigenous medical research and training resources. The centers were supported in fiscal year 1962 by grants totaling $2,093,000 to the five American universities concerned. These grants cover costs for a 1-year period, against an overall commitment for 5 years' support.

The initial phase of program development has been completed for each of the centers, and research is now being actively pursued at each foreign site. This involved the administratively complex job of concluding agreements satisfactory not only to the two private institutions involved in each case, but also meeting the requirements of the United States and the foreign government concerned. Staffing also was involved, and each of the centers has been unusually successful in attracting well-trained young scientists interested in experience and careers in international research. Each of the centers will be moderately expanded in the second phase through staff additions so that a multidisciplinary team approach can be brought to bear on the complex biomedical problems at the foreign research sites.

International Research Associates Program

This new program, which goes into operation in fiscal year 1963, was developed to assure that there will be available to the Public Health

Service an adequate number of highly capable internationally oriented U. S. investigators. This has been done by broadening the present research associate program of NIH to permit assignment of 8 to 10 Public Health Service commissioned officers each year to research projects carried out overseas by PHS units or to projects of special interest to the Service carried out by other organizations. Thus research experience and training of high quality and interest can be assured, and at the same time fulfill an important need of the PHS by supplying additional skilled manpower in support of foreign projects. The budget for fiscal year 1963 amounts to $150,000.

International Medical Science Communications

Major support is being given by NIH to three of the four basic elements or functional processes involved in biomedical communications: the personal interchange among scientists, publication of findings, and the training and educational process.

Formal meetings, seminars, symposia and other activities arranged by scientific, professional, and related organizations, which form the basic framework of the process of personal interchange among scientists, have come to have major importance in international scientific communications. As an integral part of many NIH programs and activities, support is provided for this important personal interchange process as a basic means of enlarging communications in biomedical sciences. In fiscal year 1962 NIH awarded 46 grants totaling $480,000 for support of international meetings in the United States and abroad which were organized by scientific and professional organizations. Participation in such international meetings is also permitted by allowing investigators upon specific approval to use research grant funds for travel to international meetings. This is a change from the previous policy of relying on the local institution to determine the necessity for attendance at international meetings according to its internal policy. Further study of foreign travel by grantees is underway.

It has been estimated that 60 percent of world biomedical research literature is in languages infrequently read by American scientists. Thus an important international objective of the Public Health Service (the National Institutes of Health and the National Library of Medicine, specifically) is to find means of encouraging the translation and publication of foreign literature of importance to American medical science. NIH support of primary publications, bibliography, and abstracts (e.g., Cancer Chemotherapy Reports, Psychopharmacology Abstracts, World Neurology) makes a major contribution to international science communications. Specific support of foreign institutions for translation abroad, abstracting and publication of the less accessible medical literature in fiscal year 1962 included eight grants to Excerpta Medica Foundation in Amsterdam, amounting to $237,000.

Administration

Responsibility for policy formation, program analysis, and coordination of foreign and international activities of the National Institutes of Health is in the Office of International Research, a staff arm of the Office of the Director, National Institutes of Health. Creation of this Office was motivated by the need for special attention to these activities which have expanded rapidly in magnitude and complexity in recent years, and to give specific expression to the purposes stressed in the International Health Act of 1960. The Office of International Research directly administers the special foreign currency program financed from Public Law 480-derived funds, the international centers for medical research and training, the international postdoctoral fellowship programs, the visiting scientist program, and the new international research associate program, all of which have been discussed above.

To fulfill its responsibility for evaluating medical research and scientific manpower opportunities not available in the United States and to stimulate the flow of information on medical research underway in other countries, NIH now has established overseas offices and scientific representatives in Paris for Western Europe, London for the British Isles, Rio de Janeiro for Latin America, Tokyo for the Pacific area, and New Delhi for south Asia.

Budget Summary
Operating Level - FY 1963

Grants		
Research - ICMRT		$3,692,000
Fellowships - Foreign		1,200,000
		$4,892,000
Direct Operations		
International Research		$1,012,000
Training Activities (IRAP)		150,000
	Total Direct	$1,162,000
	Total	$6,054,000

United States Public Health Service - NATIONAL INSTITUTES OF HEALTH
Table I - Principal International Activities, By Program, Fiscal Year 1962

Activity	Number of Awards	Amount
TOTAL		$29,675,603
Support of Medical Research - Total		17,449,113
Research project grants		
to investigators in foreign countries	774 grants	11,793,859
to international organizations	30 grants	1,411,559
Research contracts with foreign organizations	5 contracts	173,616
Collaborative agreements financed under Public Law 480	29 projects	3,017,624
Foreign scientists & research associates under Visiting Program	190 scientists	1,052,460
Support of Research Training - Total		11,872,242
Americans studying abroad under Fellowship program	243 fellowships	1,804,786
Americans studying abroad under Traineeships	36 traineeships	402,062
Foreign institutions receiving Training Grants	13 grants	380,299
Foreign research fellows studying in the U.S.	92 fellowships	692,095
Estimated foreign research trainees under Training Grants to U.S. research institutions	1250 trainees	6,500,000
International Centers for Medical Research & Training	5 grants	2,093,000
Support for Medical Research Communications - Total		354,243
Grants to International Professional Organizations located abroad for support of international meetings	4 grants	116,992
Grants to support translation abroad and publication of foreign medical literature	8 grants	237,251

Note on Coverage - Does not include direct operation of research laboratories in Ghana, the Canal Zone, Malaya and East Pakistan; projects conducted in cooperation with other Federal Agencies through the Interdepartmental Committee on Nutrition in the National Defense; field trials and investigations overseas conducted as an incidental part of intramural and domestic grant projects (e.g., the pilot study in Upper Volta of immunization by attenuated measles vaccine involving two trips by a NIH team of virologists). The figures on grants supporting international meetings cover only grants to professional organizations located abroad; the total of such grants to domestic and foreign organizations was 46 and the amount $840,262.

Office of International Research
National Institutes of Health
January 15, 1963

United States Public Health Service - NATIONAL INSTITUTES OF HEALTH

Table II. Selected Major International Activities by Program and Country, Fiscal Year 1962

Country	Research Grants		Research Contracts		Visiting Scientists		U.S. Fellows Abroad		Traineeships Abroad		Training Grants		International Research Fellows	
	Number	Amount	Number	Amount	Number	Amount	Number	Amount	Number	Amount	Number	Amount	Number	Amount
TOTAL	816	$13,559,661	5	$173,616	190	$1,052,460	243	$1,804,786	36	$402,062	13	$380,299	92	$692,095
Western Hemisphere - Total	196	3,312,944	2	128,866	18	86,957	17	103,112	1	8,800	8	240,969	26	188,165
Canada	108	1,863,997	-	-	7	30,469	12	71,255	1	8,800	6	147,019	-	-
Latin America - Total	88	1,448,947	2	128,866	11	56,488	5	31,857	-	-	2	93,950	26	188,165
Argentina	16	202,368	-	-	1	7,000	-	-	-	-	-	-	1	9,120
Brazil	13	123,478	-	-	4	15,088	-	-	-	-	1	32,400	4	28,347
Chile	10	105,195	-	-	1	7,820	-	-	-	-	-	-	3	18,305
Colombia	4	32,763	-	-	1	11,155	-	-	-	-	-	-	4	30,659
Costa Rica	1	7,475	1	21,000	-	-	-	-	-	-	-	-	2	13,910
El Salvador	1	14,795	-	-	-	-	-	-	-	-	-	-	-	-
Guatemala	1	7,500	-	-	-	-	-	-	-	-	-	-	-	-
Jamica	-	-	-	-	1	4,165	-	-	-	-	-	-	1	6,264
Mexico	15	205,808	1	107,866	-	-	4	26,227	-	-	1	61,550	2	16,643
Panama	6	175,512	-	-	-	-	-	-	-	-	-	-	-	-
Peru	12	359,672	-	-	-	-	-	-	-	-	-	-	4	30,328
Uruguay	6	107,441	-	-	3	11,260	-	-	-	-	-	-	3	20,659
Venezuela	3	106,940	-	-	-	-	1	5,630	-	-	-	-	2	13,930
Europe - Total	354	5,357,206	2	32,250	79	410,101	207	1,542,672	33	371,402	3	91,400	43	298,058
Austria	8	50,088	-	-	3	21,823	-	-	-	-	-	-	4	24,993
Belgium	16	212,609	-	-	-	-	3	18,621	-	-	-	-	-	240[1]
Denmark	21	190,026	1	14,750	2	3,680	14	95,132	3	31,500	-	-	2	16,141
Finland	18	175,410	-	-	3	417	-	-	-	-	-	-	4	30,686
France	44	872,547	-	-	2	6,187	22	173,850	2	20,625	-	-	1	417
Germany, Fed. Rep. of	11	82,720	-	-	12	68,576	17	142,335	3	32,990	-	-	3	23,109
Greece	2	14,775	-	-	1	7,500	-	-	-	-	-	-	1	7,342
Iceland	2	35,528	-	-	-	-	-	-	-	-	-	-	-	-
Ireland	7	64,001	-	-	1	1,749	-	-	-	-	-	-	3	20,484
Italy	30	327,709	1	17,500	12	66,669	9	59,934	-	-	-	-	4	28,523
Netherlands	13	148,324	-	-	2	21,181	4	27,922	-	-	1	41,000	1	8,640
Norway	9	98,326	-	-	1	5,670	3	17,648	-	-	-	-	1	7,216
Poland	-	-	-	-	1	1,772	-	-	-	-	-	-	3	24,757
Portugal	1	8,855	-	-	-	-	-	-	-	-	-	-	-	-
Spain	2	13,680	-	-	2	7,603	-	-	1	9,010	-	-	3	16,373
Sweden	67	1,336,505	-	-	5	30,405	31	234,095	7	74,074	2	50,400	4	32,421
Switzerland	14	172,963	-	-	8	46,405	14	108,454	-	-	-	-	-	1,040[1]
United Kingdom	87	1,521,140	-	-	22	113,796	90	664,681	17	203,203	-	-	4	25,349
Yugoslavia	2	32,000	-	-	2	6,668	-	-	-	-	-	-	5	30,3[illegible]
Africa - Total	21	465,322	-	-	3	22,145	-	-	-	-	-	-	1	8,46[illegible]
Congo, Rep. of	1	10,235	-	-	-	-	-	-	-	-	-	-	-	-
Kenya	1	17,180	-	-	-	-	-	-	-	-	-	-	-	-
Liberia	3	110,171	-	-	-	-	-	-	-	-	-	-	-	-
Nigeria	2	92,300	-	-	-	-	-	-	-	-	-	-	-	-
South Africa, Rep. of	12	193,811	-	-	3	22,145	-	-	-	-	-	-	1	8,463
Tanganyika	2	41,625	-	-	-	-	-	-	-	-	-	-	-	-
Middle East - Total	78	1,176,342	-	-	16	86,236	7	64,326	1	8,860	-	-	5	45,429
Iran	-	-	-	-	1	4,500	-	-	-	-	-	-	2	19,300
Israel	60	951,466	-	-	9	38,956	6	56,922	-	-	-	-	3	26,129
Jordan	1	54,459	-	-	-	-	-	-	1	8,860	-	-	-	-
Lebanon	16	161,187	-	-	2	22,970	1	7,404	-	-	-	-	-	-
Turkey	1	9,200	-	-	2	12,812	-	-	-	-	-	-	-	-
United Arab Rep.	-	-	-	-	2	6,998	-	-	-	-	-	-	-	-
South Asia & Far East - Total	125	1,482,345	1	12,500	71	410,546	12	94,676	1	13,000	2	47,930	17	151,980
Australia	26	483,554	-	-	5	23,304	5	40,866	1	13,000	-	-	3	27,755
Hong Kong	1	9,214	-	-	-	-	-	-	-	-	-	-	-	-
India	6	54,646	-	-	18	114,953	1	5,975	-	-	-	-	2	16,410
Indonesia	-	-	-	-	1	12,470	-	-	-	-	-	-	-	-
Japan	82	868,543	1	12,500	40	215,322	5	40,965	-	-	2	47,930	3	24,852
Korea	2	15,012	-	-	1	7,497	-	-	-	-	-	-	-	-
Malaya	1	10,791	-	-	-	-	-	-	-	-	-	-	-	-
New Zealand	2	12,090	-	-	1	9,000	1	6,87					3	26,966
Pakistan	-	-	-	-	3	17,626	-	-					1	8,770
Philippines	2	12,990	-	-	1	1,374	-	-					1	9,708
Taiwan	-	-	-	-	1	8,000	-	-					3	29,639
Thailand	3	15,195	-	-	-	-	-	-					1	7,880
Stateless - Total[2]	-	-	-	-	3	36,975	-	-					-	-
International Organizations - Total	42	1,765,802	-	-	-	-	-	-					-	-
World Health Organization	4	330,000	-	-	-	-	-	-					-	-
Pan American Health Organization	8	365,110	-	-	-	-	-	-					-	-
Institute of Nutrition of Central America and Panama	12	378,249	-	-	-	-	-	-					-	-
Excerpta Medica Foundation	8	237,251	-	-	-	-	-	-					-	-
First Asian & Oceanian Congress of Neurology	1	25,992	-	-	-	-	-	-					-	-
Fourth World Congress of Cardiology	1	30,000	-	-	-	-	-	-					-	-
International Brain Research Organization	2	48,500	-	-	-	-	-	-					-	-
International Union Against Cancer	1	58,333	-	-	-	-	-	-					-	-
International Union For Health Education	1	57,000	-	-	-	-	-	-					-	-
World Federation of Neurology	3	230,182	-	-	-	-	-	-					-	-
World Federation of Neurosurgical Societies	1	5,185	-	-	-	-	-	-					-	-

[1] Supplements to prior awards.
[2] Former citizens of Hungary, Latvia, and China.

Office of International Research
National Institutes of Health
January 7, 1963

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